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THE LOW SALT SYNDROMES *

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SOME of the earlier workers noted the presence of low levels of serum sodium or serum total base in pneumonia, diabetes mellitus, eclampsia, uremia, congestive heart failure, cirrhosis and miscellaneous other conditions.[1a, b] Schroeder's clinical report in which the phrase "low salt syndrome" was first used pointed out the concurrence of hyponatremia, azotemia and clinical deterioration in edematous patients maintained on low sodium regimens with or without excessive administration of water.[1c] In keeping with Schroeder's original description, the term "low salt syndrome" has become in subsequent usage a general phrase for all instances of low serum sodium levels. In the interim our understanding of sodium and water metabolism has increased sufficiently to establish the existence of various types of "low salt syndrome." These should now be described in specific terms indicative of particular disturbances in sodium metabolism. This will provide insight into their origins and clues to corrective therapy. Under such an arrangement the general classification "hyponatremia" might be used to refer to all abnormally low concentrations of sodium in plasma, irrespective of etiology, and perhaps replace the somewhat misleading designation, "low salt syndrome."

I. A WORKING CLASSIFICATION OF CLINICAL AND EXPERIMENTAL HYPONATREMIA

In table 1 it has been indicated that hyponatremia may be present with decreased, intact or increased total stores of extracellular sodium. Appreciation of this fact is indispensable in any discussion of the origin, the

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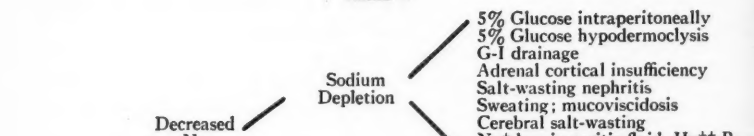
clinical significance and the therapeutic indications of hyponatremia. An attempt at the proper classification of each instance of hyponatremia in accordance with this scheme will assure adequate sodium replenishment when it is indicated and avoid useless or actually harmful sodium therapy when it is not needed.

A. Hyponatremia with Sodium Stores Decreased

1. Hyponatremia as a result of sodium depletion: The experimental production of sodium depletion described by members of this group and by others [2a–k] clearly illustrates the body fluid changes and the physiologic

TABLE 1



effects which accompany the abrupt removal of sodium from the extracellular fluid. The introduction of sodium-free aqueous solutions of glucose intraperitoneally, as first reported by Darrow et al.,[2-1] is followed by a transfer of sodium, chloride and other extracellular solutes into the peritoneal cavity. Drainage of this fluid prior to absorption results in permanent removal of these extracellular solutes from the body and reduction in the tonicity in the interstitial space and plasma as manifested by hyponatremia, hypochloremia and lowered levels of the other solutes.[2b-2f] This is accompanied by transfers of water into cells in response to the reduction in the osmotic pressure in the surrounding fluid.

When of sufficient magnitude, such changes in the volume of the composition of the extracellular and cellular phases of the body fluids result in

a loss of circulatory efficiency. This is manifested by decreases in the cardiac output, the blood pressure and the speed of the circulation.[2f] These are mediated through losses in the volume of circulating plasma,[2g] and perhaps through decreases in circulating proteins as a result of extravascular segregation.[2f, k] The viscosity of blood increases, and the tone or peripheral resistance in the blood vessel rises. The cellular overhydration which accompanies this type of experimental sodium depletion plays no detectable rôle in the shock state.[2m] This sequence of events can also be produced by dialysis of blood against low electrolyte solutions through the intervening cellophane of an artificial kidney.[2n]

There are a number of clinical situations in which an identical type of hyponatremia and depletion of extracellular solutes may result. Thus the use of low electrolyte concentrations in an immersion bath employed in treating extensive skin burns,[3a] or in vivodialysis,[2n] has been shown to produce depletion and circulatory collapse. Presumably the same results would be obtained in therapy of renal failure via peritoneal lavage with hypotonic solutions. Moreover, there are many instances of the production of sodium depletion by irrigation of the stomach or bowel by fluids free of sodium. The most common of these by far is gastric lavage employing multilumen tubes and 5% solutions of glucose in water.[3b, c] In all of the above illustrations, extracellular electrolyte is lost permanently from the body. However, temporary segregation of sufficient sodium and other extracellular solutes, as in unabsorbed glucose hypodermoclysis, will produce identical circulatory changes.[4a-d]

Other clinical situations which do not closely duplicate experimental salt depletion may still result in salt losses and produce circulatory deterioration. Losses of extracellular electrolytes in (a) urine, as in adrenocortical insufficiency,[5a-c] salt wasting nephritis and the recovery phase of acute tubular damage or lower nephron nephrosis,[6] cerebral salt wastage,[7a-f] excessive mercurial[8a-e] or other forms of diuresis, including the uncontrolled glycosuria of diabetes mellitus;[9a, b] (b) in gastrointestinal secretions as in vomitus, biliary or pancreatic drainage, uncontrolled ileostomy drainage or diarrhea,[10a-g] excessive cation exchange resin therapy;[11] (c) in sweat, and especially in that seen in mucoviscidosis;[12a, b] or (d) in transudates and exudates,[13a-d] including those from traumatized or burned surfaces, all deplete the body of extracellular sodium and chloride. In these conditions, however, one is no longer dealing with a pure or uncomplicated electrolyte loss, but with combinations of electrolyte and water deficits. If the latter are the greater, hypotonicity and hyponatremia of the body fluids will disappear and may even be replaced by hypernatremia. Hence it is important to emphasize that, though hyponatremia may be a sign of salt depletion, it is the relative deficits of sodium and water which determine the prevailing level of extracellular sodium. There is no evidence, however, that this in any way ameliorates the harmful effects of extracellular depletion; as a matter of fact, it may actually prove aggravating.[14]

2. Hyponatremia as a manifestation of chronic cellular hypo-osmolarity: Winkler and Crankshaw were among the first to report that patients with pulmonary tuberculosis and other forms of chronic lung disease may have hypochloremia and hyponatremia unresponsive to sodium chloride therapy.[15a-f] It seems probable that this represents a decrease in the osmotic activity of cell constituents, as defined by Elkinton, Winkler and Danowski,[16a-b] with a secondary extracellular hypo-osmolarity. It has also been suggested that renal adjustments play a part.[15d] Irrespective of whether the kidneys participate in a primary or a secondary rôle, it is clear that in some patients with tuberculosis extracellular sodium concentrations and total amounts are decreased but are not accompanied by the same physiologic changes produced by abrupt sodium depletion. The fact that such asymptomatic hyponatremia is not confined to tuberculosis suggests that it may be a function of some other variable, such as starvation.[16c]

An extracellular depletion of sodium may also result from a combination of transfers of sodium into cells or other depots and hypo-osmolarity. Thus it has been amply demonstrated that depletion of cell potassium is often accompanied by increases in cell sodium.[17] If this has occurred at the expense of extracellular sodium, replenishment of such potassium deficits returns the sodium to the extracellular fluid and corrects the hyponatremia.[18] This type of hyponatremia must be dependent upon or be accompanied by cellular hypo-osmolarity, or segregation of sodium in bone; otherwise, losses of sodium and water from extracellular fluid would be iso-osmotic and could not produce hyponatremia.

B. Hyponatremia with Sodium Stores Intact

1. Water intoxication in oliguric-anuric patients: The forcing of fluids beyond renal excretory capacities is a common cause of hyponatremia in oliguria and anuria. It is true, of course, that in an adult with previously intact renal function reduction in urine volumes to 350 or 250 c.c. for 24 hours with high specific gravity is highly suggestive of dehydration. In such patients, trial of several liters of oral or parenteral fluids is indicated. Such therapy is also justifiable, though usually less productive of urine flow, when greater degrees of oliguria or actual anuria supervene. However, if urine flow is not increased following such measures the probable existence of renal disease of recent onset, such as acute tubular damage or acute cortical necrosis, urologic obstruction or terminal chronic renal failure, is probable. Continued forcing of fluids in an attempt to induce a diuresis is both unwise and dangerous. It is nonetheless a common practice. Since glucose solutions are usually employed in such ill-guided attempts, hyponatremia with salt stores intact is the inevitable result. Continued administration of such fluids in excess of the body's excretory capacities ultimately results in water intoxication and convulsions.[19a-b] This form of hyponatremia can be readily avoided by limiting fluid input to volumes needed

to meet renal and extrarenal losses once the therapeutic trial has proved fruitless. Serial body weights are an excellent guide in this regard, since in such patients body weight should not be allowed to increase. As a matter of fact, a slight daily decrease, representing utilization of body fat and protein, should be the goal.

2. Postoperative water intoxication: It has been noted that preoperative medication, anesthesia and surgery itself are followed by a decrease in the capacity to excrete water. Under ordinary circumstances a child or an adult can readily dispose of some 3 L. of water per square meter of body surface in each 24 hour period, but following surgery this ceiling is reduced.[19c-e] If this tolerance is exceeded during fluid therapy, water intoxication can result.

3. Experimental water intoxication: The injection of Pitressin for a sufficiently long period during continued intake of ordinary volumes of water will also produce excessive retention of water and the dilutional type of hyponatremia.[20a-c] This is, however, of limited duration, since after several days a diuresis of water, sodium and chloride ensues, with jettisoning of the water load at the price of some depletion of these two electrolytes.

4. Asymptomatic hyperlipemic hyponatremia: It is important to realize that there is still another type of hyponatremia coexistent with intact body sodium stores. It is encountered in patients with massive hyperlipemia or hypercholesterolemia, as in diabetic acidosis and coma and in the nephrotic forms of glomerulonephritis.[21] This is merely a reflection of the fact that a given aliquot of such serum contains less water and less electrolytes because of the undue proportion of space occupied by the lipid. The hyponatremia is asymptomatic and does not, of course, require sodium therapy. On the other hand, one must be sure of such a diagnosis, since sodium depletion is not uncommon in these two entities and water excesses may produce hyponatremia in either.

C. Hyponatremia with Sodium Stores Increased

1. Clinical: As experience with hyponatremia has accumulated it has become evident that there are instances of hyponatremia which are neither of the salt depletion, hypo-osmolarity overhydration or hyperlipemic type. These are usually seen in seriously ill patients in whom edema or anasarca is present. Increasing numbers of this type of hyponatremia have been encountered in intractable congestive heart failure and in far-advanced renal failure, as well as in nephrosis.[22a-j] It has been found that this form of hyponatremia is virtually unresponsive to sodium, and that such therapy merely serves to aggravate the edema and is productive of thirst. Preliminary observations indicate that vivodialysis is without uniform benefit.[23a, b] In general, the appearance of such abnormally low serum sodium values in patients with decompensated heart, liver or renal function is an extremely ominous sign.

It seems probable that these observations of sodium metabolism result from disturbances in the mechanisms which regulate the volume, composition and distribution of body fluids. In essence, they represent a resetting of these regulators at new levels as a manifestation or consequence of the underlying disease. They may be referred to in the generic sense as "new steady states," despite our lack of knowledge about their precise mode of origin.

It is logical to raise the possibility that this form of hyponatremia is mediated through increased secretion, effectiveness or survival of antidiuretic substances,[24a] but results of clinical trials of pitressin and of measurements of circulating levels of antidiuretic substances argue against this explanation.[24b-e] Do they then represent changes in hydration, in cell osmolarity, in the extracellular position of sodium, or renal, adrenal, or nervous system regulation of body fluids?

TABLE 2

Probable Status of Extracellular and Cellular Sodium and Water in the Pure Forms of the Major "Low Salt Syndromes"

	Total Na	Extracellular Na	Cell Na	Extracellular H_2O	Cell H_2O	Plasma Volume	Peripheral Edema
Sodium depletion	Decr.	Decr.	Prob. Decr.	Decr.	Incr.	Decr.	No
Cellular hypo-osmolarity	Decr.	Decr.	?	?Intact	?Intact	?Intact	No
Water intoxication	Intact	Intact	Intact	Incr.	Incr.	Incr.	May be present
Massive hyperlipemia	Intact	Intact	Intact	Intact	Intact	Intact	No
"New steady states"	Incr.	Incr.	Incr.	Incr.	Incr.	?Incr. ?Decr.	Yes

In regard to the possible rôle of the first three of these possibilities in the production of the hyponatremia of renal failure, experimental data obtained in animal studies are available. The work of Brown et al. with dogs deprived of renal function by ureteral ligation [24f] suggests that within the first few days of anuria hyponatremia does not appear unless food and fluids are given and vomiting develops. Recalculations of their data in our laboratory, based on chloride space, argue against release of cell water or transfers of sodium out of extracellular fluid as an etiologic factor in hyponatremia that appears early in clinical failure.

As indicated earlier, these new steady states are not benefited, and are usually aggravated, by sodium therapy. It is important, therefore, to recognize their existence and to differentiate them from true salt depletion, chronic hypo-osmolarity, simple water intoxication and benign hyperlipemic hyponatremia. The only effective therapeutic measures to date

have been those which have been successful in the partial or complete restoration of adequate function in the diseased organ, whether it be the heart, liver or kidneys.

D. Summary of Body Fluid Changes in the Various Recognized Types of Hyponatremia

In table 2 we have listed the probable status of extracellular and cellular sodium and water, together with some note of plasma volume, and the presence or absence of peripheral edema. The differentiating features of the various types of hyponatremia are cited in table 3.

TABLE 3

Differentiating Features of the Various Forms of Hyponatremia Disregarding Associated Diseases

	Symptoms and Signs	Response to Hypertonic NaCl	
		Clinical	Serum Na Concentration
Salt depletion	Lassitude, confusion, circulatory collapse, ? thirst, oliguria and azotemia	Virtually complete	Return to and maintenance at normal
Cellular hypo-osmolarity	None or ? cachexia	None except thirst	Transient rise only, with return to low values
Water intoxication	Muscle and abdominal cramps, convulsions	Control of symptoms	Increase in sodium levels, with return to normal via diuresis
Massive hyperlipemia	None referable to hyperlipemia	Presumably thirst and, if continued, confusion and other signs of hypertonicity	Transient increase in sodium, with return to previous low levels
"New steady states"	Progressive deterioration in congestive heart failure, renal failure and cirrhosis	Aggravation of congestive heart failure and of edema, ascites and of anasarca, body weight gain, thirst	Transient rise, if any, with return to previously low values

It is well to emphasize that these are working classifications. As knowledge accumulates, new types of disturbances will undoubtedly be identified, and the categories of hyponatremia increased in number, perhaps at the expense of some of the currently ill-defined and poorly understood groups.

E. Hyponatremia of Mixed Origin

It is obvious that various combinations of disturbances may coexist. Thus, water intoxication may be superimposed on salt depletion, providing a dual origin for hyponatremia. Excessive removal of sodium in con-

gestive heart failure can produce a regional sodium depletion despite continuation of edema.[25] Cellular hypo-osmolarity may develop in a prolonged illness to complicate hyperlipemic hyponatremia.

Elucidation of the probable origin or origins of a particular instance of hyponatremia requires, therefore, a careful history, an accurate clinical diagnosis and, when possible, measurements of the intake, the output, the body weight, and the solutes and water of serum; a favorable response to sodium therapy will serve to identify the instances of sodium depletion and help categorize the sodium disturbance as one with body stores of this ion depleted, intact or increased.

II. Summary of Our Clinical Experiences in the Light of the Entities of Hyponatremia Herein Presented

During 1954 our laboratory in the course of 6,462 serum sodium analyses reported 291 instances of sodium concentrations reduced to 132 mEq. per liter or lower. This represented a frequency of 4%, or approxi-

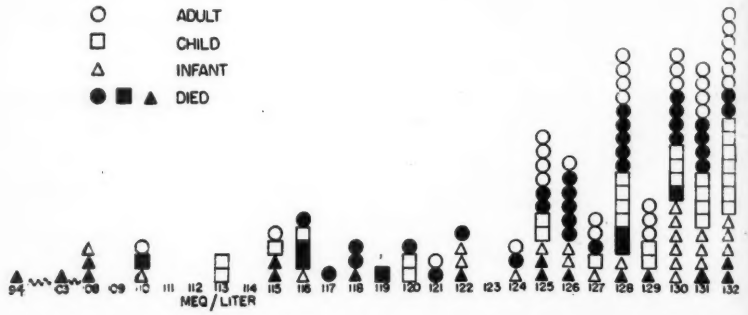


Fig. 1. Frequency of and mortality in hyponatremia. Approximately one-third of the infants and children and one-half of the adults who developed serum sodium levels of 132 mEq. per liter or less died in the course of the hospitalization.

mately one per 25 determinations. The age distribution of the 137 patients with one or more instances of hyponatremia, the degree of hyponatremia, and survival are shown on figure 1. It is readily evident that, depending on the age group, one-third to one-half of the patients who developed hyponatremia were ill with diseases that ultimately proved fatal. Hence, the appearance of low values of serum sodium may well be an ominous sign. We have therefore reviewed the clinical and laboratory findings in this group of patients and have tried to ascertain the origin or origins of the hyponatremia. In this we have relied on the clinical history, the intake and output data, the results of external balance studies and, finally, the responses to therapy. We have employed the schema of classification presented in table 1 with the following results: The commonest cause of

TABLE 4

Clinical Diagnoses and Probable Etiology of Hyponatremia Occurring in 137 Hospitalized Patients*

	Number	Sodium Depletion	Cellular Hypo-osmolarity	Water Intoxication	Hyper-lipemia	New Steady State	Unknown	Survival Living/Dead		
								Infant	Child	Adult
D.M. and acidosis	4a, 13c	4a, 11c		4a, 1c	2c				13/0	4/0
D.M. and congestive heart failure	1a					1a				0/1
D.M. and renal failure	5a	4a		2a		51				3/2
D.M. and miscellaneous	4a, 2c	1a, 1c				3a	1c		2/0	2/2
Gastrointestinal: obstruction	3a, 1c, 8i	3a, 1c, 6i		2a, 2i			1i	5/3	1/0	2/1
enterostomy	5i	5i				1i		0/5		
gastroenteritis and diarrhea	4c, 9i	3c, 6i	1i	1i			1i	6/3	3/1	
perforated viscus	2a	1a		1a						1/1
carcinoma	2a			2a		1a				0/2
miscellaneous	2a, 1c, 1i	2a		1a		1c	1i	1/0	1/0	1/1
C.N.S.: meningitis (T.B.)	2c, 2i	2c, 2i	1c, 1i					1/1	1/1	
meningitis (other)	2c, 3i	2c, 3i						3/0	2/0	
cerebrovascular accident	1a, 2i	1a, 2i		1a				1/1		0/1
brain abscess	1c	1c							1/0	
subdural hematoma	1a	1a								0/1
congenital lesions	2c, 5i	2c, 5i		1i				2/3	1/1	
Cardiovascular: congestive heart failure	3a	1a				3a				1/2
rheumatic carditis	2c					2c			1/1	
mitral valvulotomy	1a	1a				1a				0/1
subacute bacterial endocarditis	1a	1a								1/0
Renal: acute glomerulonephritis	1c					1c			0/1	
chronic glomerulonephritis	10a, 1c	4a		1a		8a, 1c			1/0	4/6
nephrotic syndrome	1a, 1c		1a		1c	1a, 1c			1/0	0/1
pyelonephritis	5a, 1c	1a		1a		4a, 1c			0/1	2/3
polyarteritis and disseminated lupus erythematosus	3a	1a				2a				2/1
lower nephron nephrosis	4a	1a		1a		3a				2/2
cortical necrosis	1a	1a								0/1
urinary tract obstruction	2a, 1i	1a				2a, 1i		0/1		1/1
Adrenal insufficiency	1a, 1i	1a, 1i						1/0		1/0
Pulmonary disease	2a, 2i	2i	2a					2/0		1/1
Miscellaneous	4a, 3c	1a, 2c		2a		1a, 1c	1a		2/1	3/1

* a, c, i refer to adults, children and infants, respectively; entries in more than one disease category were made whenever the patient had more than one major illness contributing to the hyponatremia.

hyponatremia in children was sodium depletion occurring in the course of diabetic acidosis, gastrointestinal fluid losses, and in cerebral disorders. The diabetic children invariably survived, whereas the mortality was approximately one in three in the other two groups; in the adults, hyponatremia was encountered most often in patients with cardiac or renal failure. The mortality in these groups was approximately 50% (table 4).

It should be recognized, of course, that these data are taken from a selected population, i.e., analyses of serum solute values were in general requested in patients who were seriously ill, and it may well be that other forms of unrecognized hyponatremia exist. Furthermore, the preponderance of certain disease categories to the exclusion of others obviously indicates this to be a nonrepresentative sampling. It is useful, however, as an exercise in the differential diagnosis of clinical hyponatremia.

Summary and Conclusions

Sufficient evidence has accumulated to indicate the existence of several different types of "low salt syndrome." It is useful to classify the various hyponatremias in accord with the status of the body sodium stores. The history, symptoms, signs and laboratory findings will often permit differentiation of hyponatremia resulting from sodium depletion or cellular hypoosmolarity in which sodium stores are reduced, water intoxication and hyperlipemic hyponatremia in which body sodium is intact, and the hyponatremia encountered in edema states such as congestive heart failure, cirrhosis and renal failure in which the total sodium of the body is actually increased.

Identification of the particular metabolic disturbance in body sodium and water which is present permits intelligent therapy. However, it must be emphasized that our knowledge is limited and that undoubtedly other forms of hyponatremia exist.

Summario in Interlingua

Le datos accumulate suffice pro indicar le existentia de plure differente typos de syndrome a basse concentration de sal. Il es utile classificar le varie hyponatremias secundo le stato del magazines natrial del corpore. Le historia, le symptomas, signos, e constatationes laboratorial permitte frequentemente le differentiation inter (1) le hyponatremia, resultante ab le depletion de natrium o ab hypo-osmolaritate cellular, in que le reservas de natrium es reducite, (2) le hyponatremia a intoxication aquatic e hyperlipemic in que le natrium del corpore es intacte, e (3) le hyponatremia incontrate in statos edematose, como per exemplo dysfunctionamento cardiac congestive, cirrhosis, e dysfunctionamento renal, in que le natrium total del corpore es de facto augmentate.

Le identification del disturbation metabolic de natrium e aqua que es presente in un caso specific, permitte le elaboration de un therapia intelligente. Nonobstante, nos debe insister super le facto que nostre cognoscentias in iste campo es limitate e que il existe sin dubita altere formas de hyponatremia.

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ALDOSTERONE: OBSERVATIONS ON THE REGULATION OF SODIUM AND POTASSIUM BALANCE * †

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ACCUMULATION of edema and serous effusions occurs in different clinical patterns, depending on the basic pathology. Changes in capillary pressure or colloid osmotic pressure lead to increase of interstitial fluid at the expense of plasma volume. This process alone would lead to vascular collapse rather than to edema. Retention of ingested sodium and water provides the bulk of edema and may be a useful compensation against falling plasma volume. Sodium retention may be associated with impaired renal blood flow or glomerular filtration, but in most patients the renal tubule appears to exert final control of sodium excretion. The work presented here began with a study of mechanisms which might increase renal tubular reabsorption of sodium in edematous patients.

In 1950 Deming and Luetscher [1] found strong sodium-retaining activity in lipid extracts of urine from patients with nephrosis and congestive heart failure. Although the biologic activity resembled that of desoxycorticosterone, chromatography showed that the active material was more polar.[2] In 1952 Tait, Simpson and Grundy [3] found a hormone of similar chemical and pharmacologic properties in adrenal cortical extract. Simpson et al.[4] crystallized and identified the new hormone as 18-aldehydo-corticosterone (figure 1). It was given the trivial name, aldosterone. The sodium-retaining corticoid of urine has now been crystallized and identified as the same substance.[5]

Aldosterone is more than 30 times as potent as desoxycorticosterone in reducing sodium excretion, and has a comparable effect in increasing the output of potassium. In excess, aldosterone has some properties of the glucocorticoids, such as corticosterone or hydrocortisone.[6] Aldosterone has not shown anti-inflammatory properties in the small doses thus far tested.[7]

This new hormone has been used successfully for brief periods in the treatment of Addison's disease.[8-11] Larger amounts given to a few patients with other diseases caused sodium retention and edema.[7]

Measurement of aldosterone in body fluids is difficult because of the extremely low concentration and the lack of a sufficiently specific and sensi-

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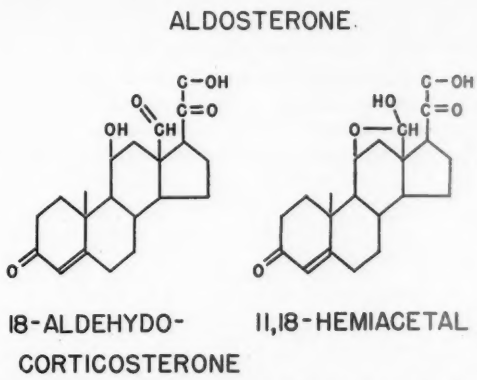

FIG. 1. Structure of aldosterone. The hemiacetal is thought to be the form present in body fluids.

tive chemical test. Systematic measurements on blood have not been made because of the great difficulties of measurement, the large volumes of blood required,[12] and the considerable diurnal variation found in urine.[13, 14] All of the studies to be presented have been made on one or more days' urine from

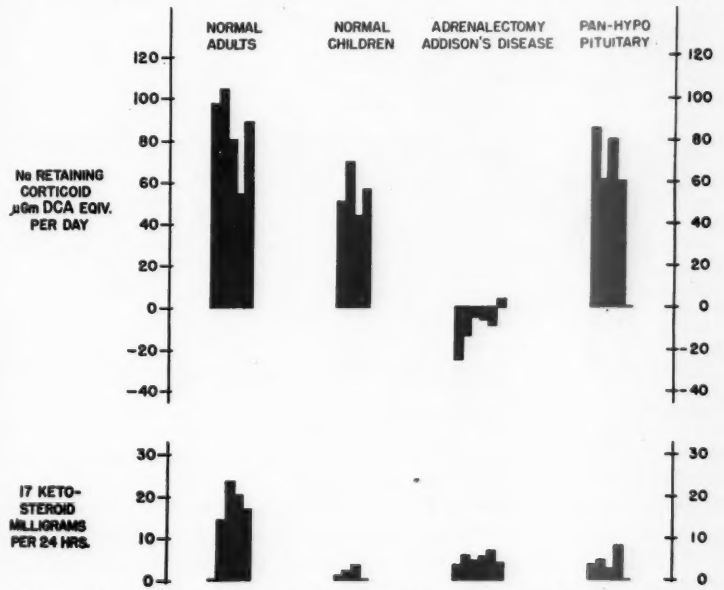

FIG. 2. Aldosterone ("sodium-retaining corticoid") in urine of normal adults and children and of patients with hypoadrenalism and hypopituitarism. Aldosterone 1 μg. = 36.5 μg. DCA equivalent in this bio-assay.

normal subjects or patients. A neutral lipid extract from acid urine is made and separated by paper chromatography.[15] The fraction containing aldosterone is assayed biologically in adrenalectomized rats.[16]

Excretion through the kidneys is not a major route of elimination of corticosteroids. When aldosterone was given to two patients, 0.4 to 4.3% of the administered hormone was recovered from the urine.* Aldosterone

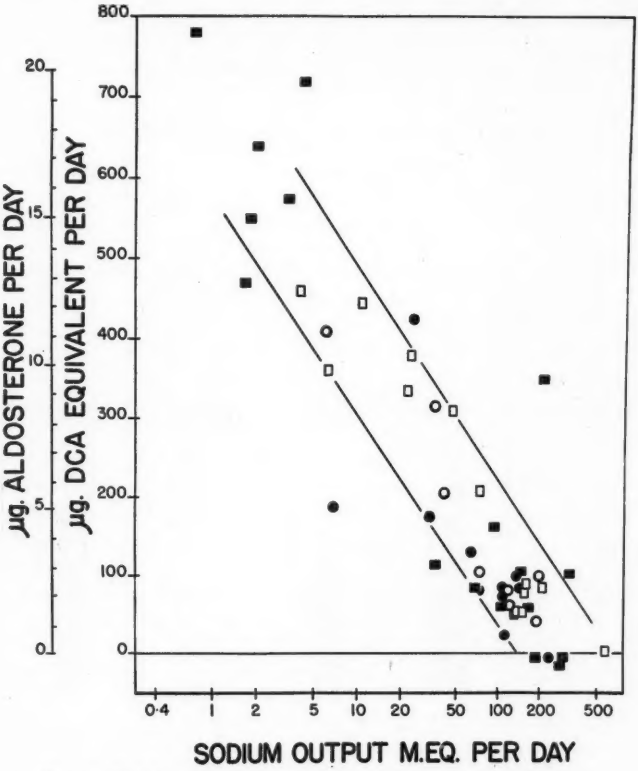

FIG. 3. Relation between aldosterone and sodium output in urine.

appears in normal amounts in urine of normally hydrated patients without obvious relation to renal function and diuresis.

There is general agreement on the very high output of aldosterone in nephrosis, congestive heart failure, cirrhosis and toxemia of pregnancy.[1, 6, 15, 17, 18] Increased aldosterone levels can be correlated with periods

* We are indebted to Dr. L. Wilkins, Dr. G. W. Thorn and their associates for making these studies possible.

of low urine sodium and accumulation of edema.[19] When improvement follows treatment of the underlying disease, the output of this hormone falls. Thus, exacerbation of these diseases appears to stimulate the secretion of aldosterone or to impair its inactivation.

Exogenous corticotropin appears to have no direct effect on aldosterone in the urine of normal men. In patients with nephrosis, the high output of aldosterone is reduced under treatment with ACTH, cortisone or serum albumin when diuresis ensues.[2] In other cases, the same therapeutic agents may neither decrease aldosterone in urine nor induce diuresis. In these

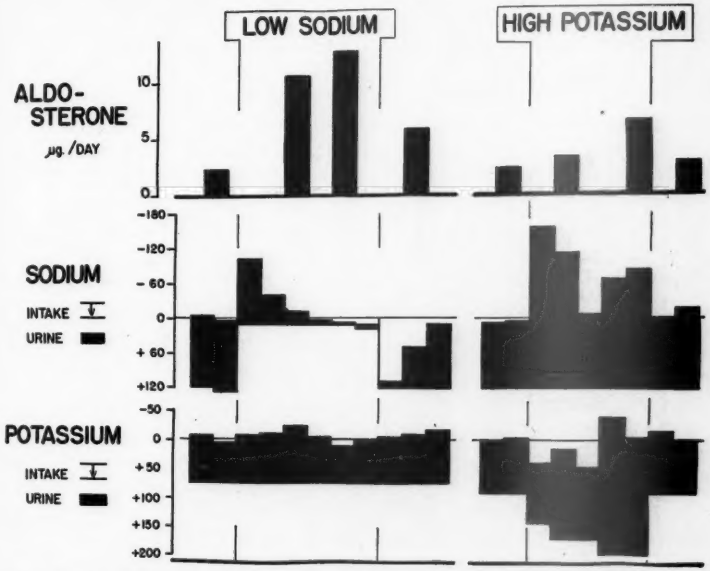

FIG. 4. Comparison of effects of low sodium and high potassium régime on aldosterone output and on balances of sodium and potassium in a healthy 41 year old man. Intake of sodium or potassium is charted down from zero line, and each day's output is indicated by height of black block. Scale shows balance in milliequivalents per day. During both experimental periods there was strongly negative sodium balance, indicated by extension of output blocks above balance line.

cases, improvement in the underlying physiologic disturbance, or some other mechanism as yet undetermined, appears to suppress the output of aldosterone.

Aldosterone is not present in urine in Addison's disease or after bilateral adrenalectomy (figure 2). Destruction or surgical removal of the hypophysis was followed by marked reduction of 17-ketosteroids and 17-hydroxycorticoids in urine; but aldosterone was found in normal amounts in urine of five of six such patients, and in significant amounts in the sixth. Thus the

measurement of aldosterone in urine may assist in the differentiation of primary adrenal insufficiency from that form which is secondary to pituitary failure.*

Large changes in sodium intake are followed by significant inverse changes in output of aldosterone. In figure 3, open squares and circles, indicating normal men and women, are included within limits indicated by the

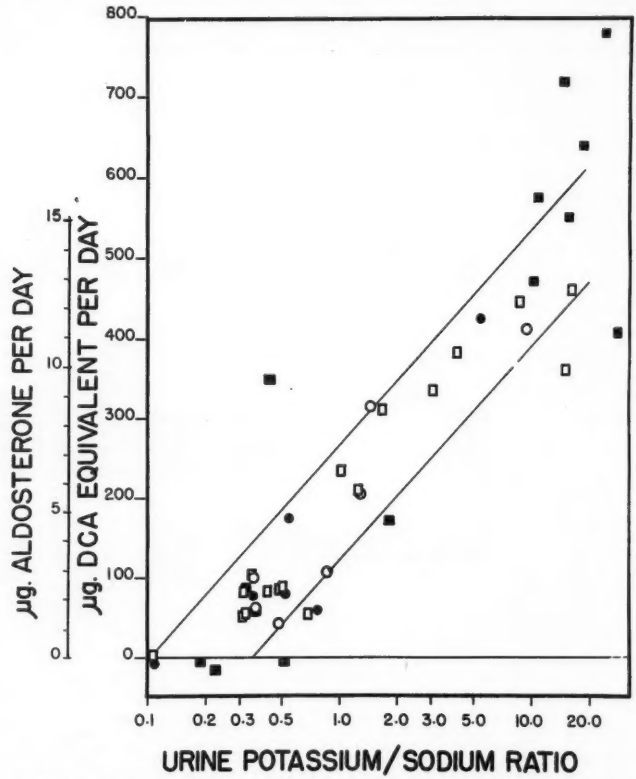

FIG. 5. Relation between aldosterone output and potassium to sodium ratio in urine.

lines. The cluster of values about 100 to 200 mEq. sodium and 1 to 3 μg. aldosterone per day represents subjects in balance on normal diets. The normal increase in aldosterone output on low sodium diets is indicated by the higher values between the lines. The absence of measurable aldosterone on a very high sodium intake is also demonstrated in a normal subject and

* In myxedema, also, aldosterone is found in normal or increased amount, while the other adrenal hormones are greatly reduced.

a patient. Other very low values for aldosterone are from patients with Addison's disease. Very high aldosterone levels, shown by solid squares and circles in upper area to left, are from patients with congestive heart failure, hepatic cirrhosis and nephrotic syndrome. Two aberrant solid squares to right of normal range show high output of aldosterone and sodium in a case of sodium-losing nephritis. The aberrant circle to the left of the normal range shows the definite but limited increase in aldosterone output in a hypophysectomized patient on low sodium diet.

Increased potassium intake may also lead to increased output of aldosterone. In a normal man (figure 4), ingestion of potassium chloride was followed by loss of sodium and by significant increase in level of aldosterone. There is evidence that potassium deficiency may decrease secretion of aldosterone,[23] but we have observed that in the hypokalemic alkalosis of pyloric obstruction, increased aldosterone output may occur. It is possible that potassium in certain circumstances may exert some control over the output of aldosterone directly, in addition to its complex effects on sodium balance. If the output of aldosterone is compared with urine potassium, a poor correlation is observed; but a good correlation is found with potassium to sodium ratio. This is not unexpected, since the bio-assay of aldosterone depends upon the change in potassium to sodium ratio in the urine of adrenalectomized rats.[16] Man's response to his endogenous aldosterone may be expressed in the same way, as shown in figure 5.

Discussion

These data indicate that there is a close correlation between aldosterone output and electrolyte balance in man. It is evident that the effect of aldosterone may vary somewhat under various conditions of renal function, electrolyte load and capillary equilibrium. This is not surprising, since the effect of other corticosteroids is conditioned by physiologic factors.

In normal man, aldosterone plays a part in renal adjustment to changes in electrolyte balance (table 1). This adaptation is impaired in primary adrenal insufficiency. Removal of the pituitary does not necessarily result in loss of this capacity;[20] aldosterone output may be increased during sodium deprivation in a patient after hypophysectomy.* In the adrenogenital syndrome and in Cushing's syndrome, the output of aldosterone is usually not far from normal.

Conn[21] and Mader and Iseri[22] have described adrenal cortical tumors which secreted a large excess of aldosterone. These patients showed hypokalemia, alkalosis and hypernatremia, which were manifested clinically as severe muscular weakness, periodic paralysis, tetany resistant to calcium therapy, hypertension, little or no edema, and signs of mild, chronic renal insufficiency. Some similar cases have been previously described as "potas-

*We are indebted to Dr. O. H. Pearson and Dr. J. P. Maclean for the opportunity to make these observations.

sium-losing nephritis"; it is now considered that they also represented cases of "primary hyperaldosteronism."

When excess aldosterone appears in a patient with heart disease, the nephrotic syndrome, hepatic cirrhosis or toxemia of pregnancy, the initial effect on the kidney is retention of sodium, and the accumulation of edema is favored by the disturbed capillary equilibrium. In this case, the high output of aldosterone is secondary to the presence of other disease, and the effects of the hormone may be modified by changes in the kidneys and in other tissues.

Aldosterone does not show its usual effects when the kidneys fail to respond. In a case of "sodium-losing nephritis," a high output of aldosterone was associated with dehydration and loss of sodium in the urine;

TABLE 1

Aldosterone Output

	Low	"Normal"	High
"Normal" Physiologic	High *Na* intake Low *K* intake ↓ Compensation	Normal *Na* and *K* balance	Low *Na* intake High *K* intake ↓ Compensation
Primary adrenal disease	Hypoadrenalism ↓ *Na* loss *K* retention	Adrenogenital or Cushing's Syndrome (?)	Adrenal tumor *K*-losing nephritis ↓ *K* loss (*Na* retention)
Heart failure Nephrosis Cirrhosis	Functional Pathology		
	Improving (+*Na* loading) ↓ *Na* loss Diuresis	Latent	Aggravated (+Low *Na* intake) ↓ *Na* retention Edema

later the output of aldosterone fell to normal in this patient when a very high sodium intake resulted in improved hydration, with very high daily excretion of sodium.*

CONCLUSIONS

Aldosterone is secreted by the human adrenal. At a physiologic level its chief effects are to decrease sodium excretion and to increase potassium excretion. The fraction which appears in an active form in urine has been measured in normal men and in various patients.

The output of aldosterone in normal men is closely related to sodium and potassium intake and balance, and suggests an effort to return the altered balance toward normal. The pituitary appears to have little control over its secretion in man.

* We are indebted to Dr. G. W. Thorn and associates for making these measurements possible.

Aldosterone output is increased: (1) in normal men on diets low in sodium or high in potassium; (2) in the nephrotic syndrome, congestive heart failure, hepatic cirrhosis, or toxemia of pregnancy during periods of exacerbation and accumulation of edema: effective treatment and improvement of the underlying condition result in reduced aldosterone output and diuresis; (3) in tumors of the adrenal cortex which secrete aldosterone.

Summario in Interlingua

Aldosterona es secernite per le glandula adrenal human. In concentrationes physiologic su principal effecto es le reduction del secretion de natrium e le augmentation del excretion de kalium. Le fraction de aldosterona que appare in forma active in le urina ha essite mesurate in homines normal e in varie patientes.

Le rendimento de aldosterona in homines normal es strictemente relationate al ingestion e balancia de natrium e kalium e pare servir le objectivo de reverter balancias alterate verso le norma. Le glandula pituitari human pare exercer pauc influentia regulatori super le production de aldosterona.

Le rendimento de aldosterona es augmentate (1) in homines normal qui recipe dietas a basse contento de natrium o a alte contento de kalium; (2) durante periodos de exacerbation e de accumulation de edema in patientes del syndrome nephrotic, de congestive dysfunctionamento cardiac, de cirrhosis hepatic, o de toxemia de pregnantia; efficace therapias que meliora le subjacente conditiones resulta in un reducite secretion de aldosterona e augmentate diurese; e (3) in patientes con tumores adrenocortical que secerne aldosterona.

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THE PRESENT STATUS OF ACTH AND ADRENAL STEROID THERAPY IN MEDICINE *

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In this era, with important new medical advances proceeding at such a rapid rate, it is often difficult to afford a new discovery its rightful place. However, the majority would agree that a sense of being on the threshold of a great achievement greeted the announcement of the clinical effects of ACTH and cortisone in rheumatoid arthritis and rheumatic fever by Hench [1, 2] and his collaborators in 1949. This is particularly true if one recalls the first clinical ACTH Conference, at which time most observers felt that a revision of the present concept of many diseases was necessary. Since these hormones seemed to affect such a wide spectrum of diseases, they were tried as supply permitted in almost every illness known, and often preliminary favorable results required revision in the light of later experience. At the present time, some five to six years later, the value of these agents in clinical medicine is more definitely established, although their ultimate place in the therapeutic armamentarium is still being decided.

Since the initial observations on the metabolic effects of ACTH in man by Browne [3] in 1948, and on the clinical effects of ACTH and cortisone by Hench in 1949,[1, 2] there has arisen a voluminous literature which even the most ardent disciple in this field finds impossible to cope with. A recent review by Thorn [4] and his collaborators contains 673 references. I propose to discuss the effects of these agents in the diseases with which I am personally familiar, and will not attempt to mention all the circumstances in which these hormonal agents have been used, since they have made inroads into every medical discipline.

The physiologic effects of ACTH and the adrenal cortical steroids have been adequately reviewed, but it is worth while emphasizing that the safe and effective therapeutic use of these agents depends on an understanding of their physiologic effects insofar as they have been described.

That the adrenal cortical hormones are produced in response to the adrenocorticotropic hormone of the anterior pituitary is accepted fact; in the absence of the latter, adrenal atrophy occurs which can be restored to normal by the administration of ACTH. Endogenous ACTH secretion is governed by at least two factors: one, the level of circulating adrenal cortical hormones; and two, neuro-endocrine influences affecting the anterior pituitary through the hypothalamic hypophyseal system. Thus anything which leads to increased utilization of the adrenal cortical hormones in the organism lowers the circulating blood level and calls into play increased

* From the Symposium on ACTH and Cortisone, presented at the Thirty-sixth Annual Session of The American College of Physicians, Philadelphia, Pennsylvania, April 28, 1955.
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production of ACTH. A direct stimulation of ACTH production also occurs following certain stresses to the organism, which is mediated by the second mechanism. Conversely, if the level of circulating adrenal cortical hormone is high, there is an inhibition of pituitary ACTH production.

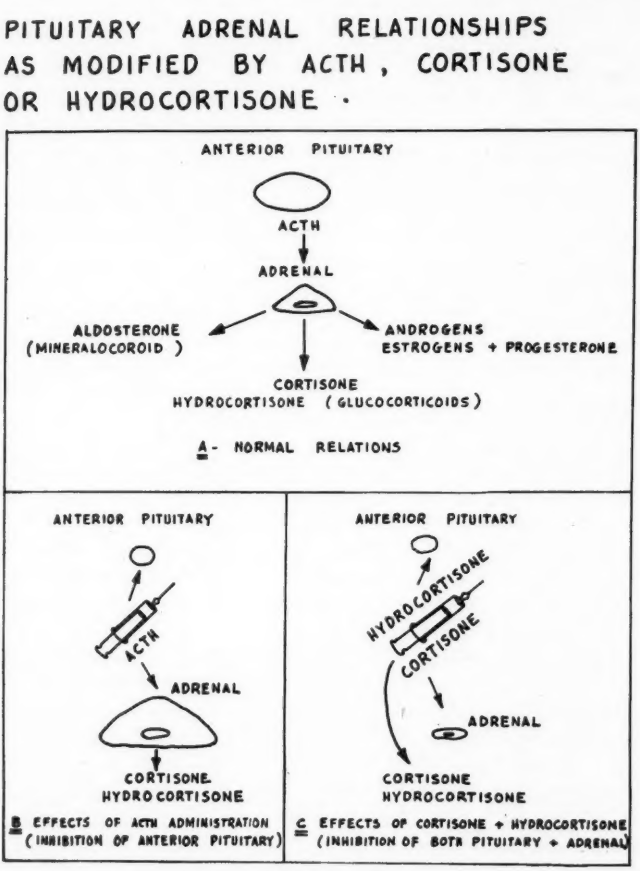

FIG. 1. Pituitary-adrenal interrelationships.

This concept has important clinical application (figure 1). With exogenous administration of ACTH there occurs a hyperplasia of the adrenal cortex with increased production of the adrenal cortical hormones, accompanied by an inhibition of endogenous ACTH production. Thus on cessation of ACTH administration a temporary endogenous ACTH deficiency results.

With cortisone or hydrocortisone administration the high level of adrenal cortical hormones inhibits endogenous ACTH production and also leads to an adrenal cortical atrophy. This is especially apt to occur during prolonged administration of these agents at the higher dose levels. On cessation of therapy a temporary adrenal insufficiency results which lasts from several days to several weeks. Failure to grasp this principle has led to unnecessary and untimely deaths of patients, since there is a tendency to stop administration when surgery, infection or any abrupt change in the patient's condition occurs and the demand for these agents increases.

Types of Hormonal Agents Available and Their Dosage Schedules

An attempt is made in table 1 to classify the types of hormonal agents available. The initial cruder preparations of ACTH were assayed in rats by the adrenal ascorbic acid depletion method and their activity was expressed in milligrams, as compared with 1 mg. of the original Armour standard L-A-1A. Since the discovery by Astwood [5] that a marked increase in purity of corticotrophin could be obtained by oxycell adsorption, more potent preparations have become available and ACTH has been marketed in units, 1 unit being equivalent to 1 mg. of the original Armour standard. Preparations of ACTH with prolonged action are marketed in clinical units dependent upon clinical assay.

The average initial dose of ACTH in most clinical disease states lies between 50 and 100 units per day, in three or four equally divided doses, or 40 to 80 units of the long-acting ACTH given once or twice daily. When remission of the disease process occurs the dosage is reduced to the smallest minimal effective one, which usually is about 40 units daily. The newer preparations can be administered either subcutaneously, intramuscularly or intravenously. In this discussion of the dosage of these hormones, averages have been mentioned; the actual dose varies with both the disease process and the individual, the correct dose being the effective one. It is important to emphasize that individualization of dosage is paramount.

Cortisone acetate is available as a suspension of microcrystals in saline for intramuscular use and as tablets for oral administration. The full clinical and metabolic effects with intramuscular administration are delayed for several days, and also persist for up to four to five days after cessation of cortisone administration. This is due to a slow release of cortisone from the intramuscular sites. Oral preparations, on the other hand, have a rapid clinical and metabolic effect, and the duration of action is short lived (from six to eight hours). It is important with oral administration to spread the dose over as much of the 24 hour period as is feasible. Initial cortisone dosage for most disease entities is 200 to 300 mg. per 24 hours, reduced over several days to 100 mg. daily. When remission has been obtained an attempt should be made to find the smallest possible maintenance

dose. Cortisone is also available in ointments for topical application, which in dermatologic disorders has met with little success; and as dilute suspensions and ointments for ophthalmologic use. Hydrocortisone is available as both the free alcohol and the acetate. It may be administered orally, intramuscularly, intravenously and intra-articularly. Its metabolic activity is approximately one and one-half to two times that of cortisone acetate, and the dosage requirements are thus halved. Intramuscular hydrocortisone acetate is relatively inert because of its insolubility. With hydrocortisone, however, there is a marked increase in its effectiveness when administered locally, and it thus has become important as a therapeutic

TABLE 1

Types of Hormonal Agents Available

ACTH *Short-Acting Preparations* (25 and 40 I.U./c.c.)

Corticotrophin—Crude U.S.P.
Corticotrophin—Purified U.S.P.

Long-Acting Preparations (20 and 40 I.U./c.c.)

Corticotrophin—Purified in 16% Gelatin
Corticotrophin—Purified in 40% P.V.P.
Corticotrophin—Purified in Zinc Phosphate Suspension
Corticotrophin—Purified in Aqueous Suspension of a Carboxymethylcellulose Complex
Beef Corticotrophin—Purified in 16% Gelatin
Lamb Corticotrophin—Purified in 16% Gelatin
Whale Corticotrophin—Purified

CORTISONE ACETATE

Aqueous Suspension for I.M. Use	25 mg./c.c. and 50 mg./c.c.
Oral Cortisone Tablets	5 mg. and 25 mg.
Ophthalmic Suspension	5 mg./c.c. and 25 mg./c.c.
Ophthalmic Ointment	1.5%

HYDROCORTISONE (Hydrocortone)

Hydrocortisone Acetate—Aqueous Suspension for Intra-articular Use	25 mg./c.c. and 50 mg./c.c.
Oral Hydrocortisone	10 mg. and 20 mg.
Intravenous Hydrocortisone Solution	20 c.c.—100 mg.
Ophthalmic Ointment	0.5% and 1.5%
Topical Ointment	1% and 2.5%

Ophthalmic and Topical Hydrocortisone Ointments and Solutions Combined with Neomycin and Terramycin.

agent in dermatologic disorders. In man, no therapeutic action of ACTH has been demonstrated which is not mediated by the liberation of the adrenal cortical steroids.

THE CLINICAL USES OF ACTH AND CORTISONE

Since these substances are hormonal agents, it seems logical that their use in *endocrine disease* be mentioned first. The advent of ACTH, and particularly cortisone, has permitted replacement therapy in panhypopituitarism and Addison's disease to reach a more nearly optimal level than has heretofore been possible. Thorn [4] and his associates have reported

extensively on the use of cortisone acetate in chronic *adrenal insufficiency,* and recommend 15 to 30 mg. daily, supplemented by desoxycorticosterone or sodium chloride to maintain an adequate electrolyte balance. We have been able to maintain our Addisonian patients on an average dose of 37.5 mg. per day, given in three divided doses orally, with the addition of 6 gm. of enteric-coated sodium chloride. Our experience with the use of DCA pellets or intramuscular DCA and cortisone has not convinced us that the addition of DCA, as such, gives any advantage except in isolated instances following total adrenalectomy in which cortisone and sodium chloride alone have not corrected the postural hypotension which some of these individuals complain of.

On the above régime the skin becomes warmer, softer and less dry; there is increased hair growth on the extremities, an increased capacity to do mental and physical work, increased appetite and weight gain, restoration of blood pressure, return of menstrual periods, fading of the mucous membrane and skin pigmentation, return of glucose tolerance curves to normal, correction of the tendency to develop fasting hypoglycemia, and reversal of the abnormalities in the electrocardiogram and the electroencephalogram. In short, these previously severely ill patients are restored to a state of health which is very near normal.

In acute adrenal insufficiency general supportive measures must still be carried out and, in addition, cortisone acetate, 200 to 300 mg. per day, must be administered, together with a wide-spectrum antibiotic to control a precipitating infection, if it be present. The use of intravenous adrenal cortical extract has largely been supplanted by intravenous hydrocortisone, which seems specific in the therapy of acute crisis. Those patients on maintenance therapy should be instructed to increase their dose when infections or other forms of increased stress are present. In the crisis which may arise following ACTH or cortisone withdrawal, a similar régime is carried out. These patients should be warned not to stop therapy because, by so doing, an extremely rapid adrenal crisis may ensue.

Several new synthetic steroids * have been used in the management of Addison's disease. We have had experience with 9α-fluorohydrocortisone in six patients previously maintained on 25 or 37.5 mg. of cortisone acetate daily, and 3 to 6 gm. of added sodium chloride (figure 2). This steroid has a potent effect on electrolyte and water metabolism, and in doses of 1 to 2 mg. resulted in edema in all cases. This was accompanied by a rise in serum sodium and a fall in serum potassium compared with their levels on cortisone acetate maintenance therapy. When the dose was reduced to 0.5 mg. the edema disappeared but the patients complained of anorexia, nausea and severe fatigue. In recent months these observations have led to a trial of a mixture of 9α-fluorohydrocortisone and hydrocortisone (0.1 mg.:5 mg.). On the basis of preliminary observations, we

* Courtesy of Dr. J. Laurie, of Merck & Co., for the supplies of 9α-fluorohydrocortisone.

believe that the optimal maintenance dose of this combination is 0.2 mg. of 9α-fluorohydrocortisone and 10 mg. of hydrocortisone. The patients feel as well as on our usual maintenance therapy and no longer need supplementary sodium chloride.

Clinical and metabolic studies on the effects of ACTH in *panhypopituitarism* have been reported by various observers. All agree that these patients can be maintained in excellent condition with parenteral ACTH administration. We have attempted to maintain two patients with pan-

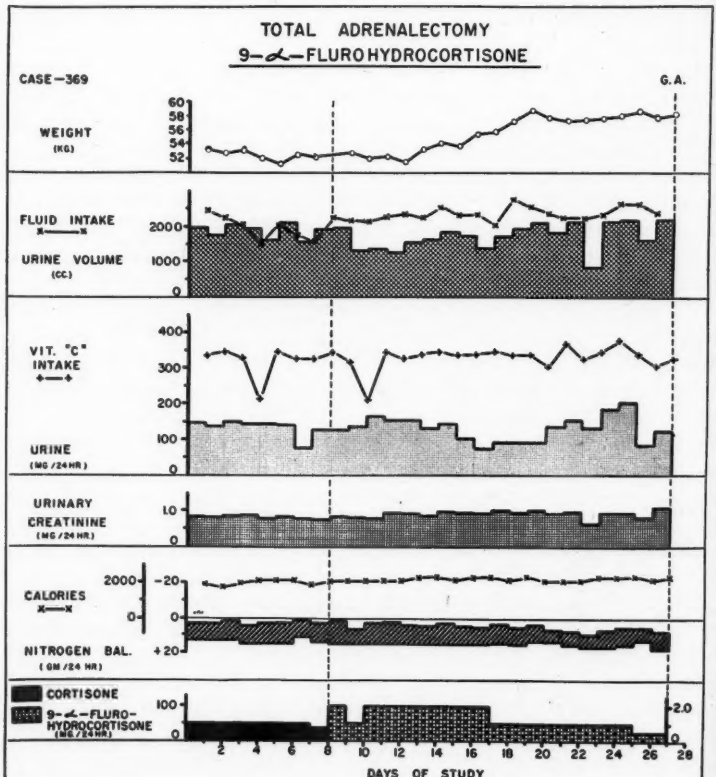

FIG. 2. Metabolic balance data during the administration of 9α-fluorohydrocortisone to a totally adrenalectomized patient. There is a horizontal base line at zero. The intake is charted downward from this base line. The urinary and fecal excretions are then measured upward from the intake line towards the base line. If the output exceeds the intake, the final level will be above the base line; if the output is less than the intake, the final level will be below the base line. Thus a negative balance is indicated by a shaded area above the base line and a positive balance by a clear area below the base line. Note particularly the fluid retention and weight gain.

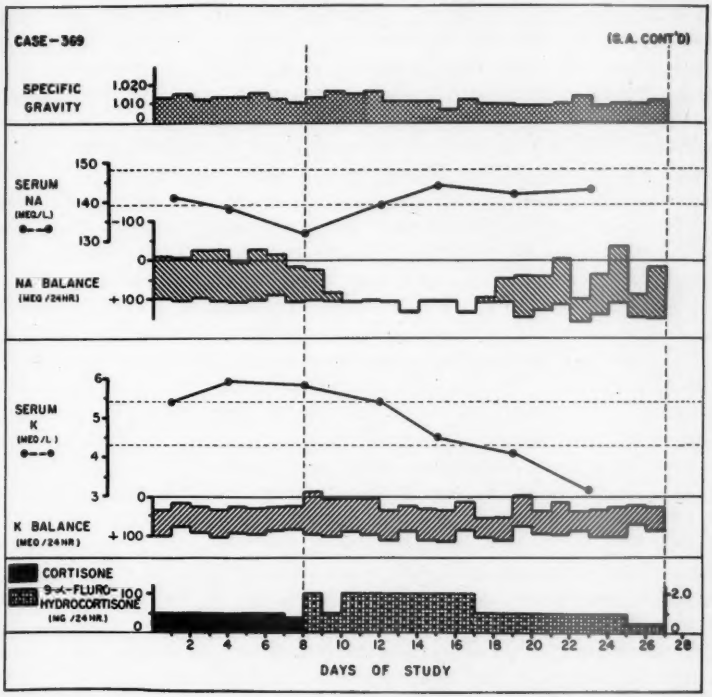

FIG. 2 (continued). Note the marked sodium retention with a rise in serum sodium. There is a fall in serum potassium to hypokalemic levels with some increase in urinary potassium excretion.

hypopituitarism on a long-acting ACTH preparation, with poor results. Steroid assays carried out during the administration of 10 units once daily showed no rise over the control levels. Oral cortisone administration, however, is more feasible, and the improvements noted in patients with Addison's disease are also seen in those with hypopituitarism. These patients, in our experience, can be returned to a relatively normal existence on a similar regimen; on the average, they require about 25 to 37.5 mg. of cortisone acetate daily. The addition of thyroid and testosterone in males, to make replacement therapy complete, is advisable. In the past five years we have prepared most of our patients for pituitary surgery with either ACTH or cortisone, and it is the impression of the neurosurgeons that their postoperative course has been very much improved.

These hormonal agents have been used in rare endocrine disturbances, such as congenital adrenal hyperplasia, and in the preparation of pancreatic

beta cell adenomata for surgery. Cortisone and hydrocortisone have made possible total adrenalectomy and hypophysectomy in malignant disease and hypertension. We have been interested, as has Conn,[6] in the use of cortisone or hydrocortisone in measuring the functional reserve of the pancreatic beta cells in patients with borderline diabetes mellitus.

Single-dose ACTH administration is of aid in making a diagnosis of adrenal insufficiency, as are the 48 hour and other modifications introduced by many workers in this field. Two criteria of response were used initially by Thorn:[7] a drop of 50% or more in the circulating eosinophils, and an increase of 50% in the uric acid excretion four hours after the administration of 25 mg. of ACTH. We have used broader metabolic criteria as evidence of response to single-dose ACTH administration in the investigation of adrenal failure (urinary sodium, chloride, potassium, uric acid, 17-ketosteroids and formaldehydogenic corticoid excretion as well as the eosinophil count). Measurement of the 17-ketosteroids and the 17-hydroxycorticoids (Porter-Silber) before and 48 hours after ACTH administration as a criterion of adrenal response to ACTH is, in our experience, the most satisfactory procedure for diagnosing adrenal cortical insufficiency.

The usefulness of the eosinophil count in studying the response to ACTH or the effectiveness of administration of the adrenal cortical steroids depends first on the technical accuracy of the individuals doing the direct count. In addition, many factors other than ACTH and cortisone affect the eosinophil count, and large daily variations in the eosinophil count occur in the same individual. We feel that single eosinophil determinations in an assessment of pituitary adrenal responsiveness should not be used as the only criterion, and that routine eosinophil counts in the practical management of patients receiving these hormones are not necessary. To be guided by the clinical response is the more obvious and better method of determining an adequate therapeutic response. If such fails, when dosage is considered adequate, then an eosinophil count can be of aid in assessing within limits the effectiveness of the hormone administration.

The observations of Hench, Kendall and their associates[1] on the beneficial effects of ACTH and cortisone in *rheumatoid arthritis* have been adequately confirmed most recently by Bunim[8] in a four year study. We have adopted the attitude that these agents should not be used to the exclusion of the well recognized therapeutic measures in this form of arthritis, but that, in properly selected cases, the hormonal agents are very useful. All agree that permanent remissions after cessation of therapy are rare indeed, and that various modifications of continuous administration must be carried out to maintain improvement.

In selection of patients, the severity and duration of the disease, the rapidity of its progression, the previous response to general medical and physiotherapeutic procedures, sensitivity to or fear of chrysotherapy, Butazolidin and other antirheumatic drugs should all be taken into consideration.

Those patients with a severe, rapidly progressive rheumatoid arthritis of relatively short duration who respond to moderate doses of the steroid are ideal candidates. In any individual, particularly one who has failed to respond to general medical measures and gold therapy but who, by the use of the hormonal agents, can be converted into a useful member of society, we feel that the administration of ACTH, cortisone or hydrocortisone cannot be denied, provided no serious contraindications to therapy exist. Restoration of patients to a state of self sufficiency is one of the most useful features of this therapy. The use of hormonal agents is of value during the initiation of physiotherapeutic procedures, as is their use combined with the administration of gold and other antirheumatic agents. It is agreed that an initial suppressive dose which is slowly and gradually reduced to the smallest feasible maintenance dose is the program of choice. Children with Still's disease usually will respond well to therapy.

As in so many other diseases, all observers have noted that the more advanced and long-standing cases require larger initial and also larger maintenance doses than the earlier, less advanced ones. It must be remembered that in the evaluation of all therapy the natural course of rheumatoid arthritis with its remission and exacerbations must be borne in mind.

Radiotherapy in Marie-Strümpell spondylitis has been so successful that we have reserved the hormonal agents for the occasional relapse. Rapid resolution of symptoms in the shoulder-hand syndrome when the patient is receiving these agents combined with active physiotherapy has also been noted.

The intra-articular administration of hydrocortisone in rheumatoid and traumatic arthritis and in osteoarthritis, where the disease is localized, is very useful, as it is in bursitis and calcific tendonitis. A dose of 10 to 50 mg. of hydrocortisone acetate is effective for from three to 21 days.

Recent observations have suggested that topical hydrocortisone in a suitable vehicle applied to areas of localized joint involvement may be useful.

The use of ACTH and the adrenal steroids in *acute gouty arthritis* has led to amelioration of the local and systemic manifestations in the majority of instances reported. This has often been followed by a recurrent attack of gout after cessation of hormone administration. We have restricted the use of these agents to those cases of gout failing to respond to colchicine in which a short course of either ACTH or cortisone induces a remission which can be maintained with colchicine.

The marked enthusiasm following Hench's [2] initial report on the effect of cortisone in the acute phase of *rheumatic fever* has been tempered by time. At present, particularly since the appearance of the Joint Report by the Medical Research Council of Great Britain and the American Heart Association,[9] a controversy has arisen concerning whether the results of

such a joint investigation actually mirror the results seen in individual cases. The Joint Report stated that there was no significant difference among the three treatment groups (ACTH, cortisone and acetylsalicylic acid) as to the status of the heart at the end of one year; that there was no evidence that any of the three agents resulted in uniform termination of the disease, and that some patients developed fresh manifestations during treatment, regardless of the type. They recognized that with either hormone there was a more prompt disappearance of the acute manifestations, but that these tended to reappear for a limited period after cessation of therapy. However, all will agree that the hormonal agents abolish most, if not all, of the signs, symptoms and laboratory evidence of rheumatic fever; the rapidity with which it occurs depends on the duration of the disease. Early diagnosis and prompt institution of therapy may lead to a more favorable response than the large combined studies would suggest. Wilson's [10] data strongly support this concept. There also seems no doubt that either ACTH or cortisone can be life-saving in severe fulminating rheumatic pancarditis, and it is perhaps here that its best use will eventually be found.

The effects of ACTH and the adrenal steroids in *allergy and hypersensitivity* have already been discussed at a Morning Lecture during the present Annual Session of the American College of Physicians. In this field these agents have been demonstrated to be important additions to the therapeutic armamentarium. Rose, of our clinic, with experience in the use of ACTH, cortisone and hydrocortisone in over 400 cases of bronchial asthma, finds these agents of great value in the management of the disease. Again it must be pointed out that the hormonal agents must not be used to the exclusion of other recognized effective forms of therapy.

Caution is needed in the use of these agents in patients with associated emphysema and cor pulmonale, since both their respiratory and circulatory difficulties may be markedly accentuated due to the retention of sodium and water.

Both hydrocortisone and corticotrophin are valuable aids in the treatment of status asthmaticus. Fifteen to 25 units of corticotrophin, given intravenously over an eight hour period, are very effective, as is intravenous hydrocortisone.

Acute drug sensitivities respond well and promptly to these hormonal agents, as do the arthralgia, urticaria and neuritis of serum sickness. Intravenous hydrocortisone is a valuable adjunct in the management of acute anaphylaxis.

The vast majority of patients with chronic urticaria, hay fever, vasomotor rhinitis and eczema respond favorably to hormonal therapy, but relapse occurs promptly on cessation of its administration.

The clinical entities which fall into the general classification of diseases of collagen vary with the individual author. In *periarteritis nodosa* improvement following hormonal therapy has been noted by many observers,

with prompt remission of symptoms and signs, but the damage already wrought by the disease process seems little affected. Schick [11] described histologically complete healing of all arterial lesions, with obliteration of the vessels resulting in multiple infarcts in the heart, kidney and gastrointestinal tract. We feel that early recognition of the disease, followed by prompt hormonal treatment for prolonged periods, is most efficacious; it must be realized, however, that residual vascular damage will remain.

In *disseminated lupus erythematosus* adequate doses of corticotrophin or the adrenal steroids will cause a remission of fever, arthritis, skin and mucous membrane lesions, pleuritis, pericarditis and the anemia in the majority of patients. The L.E. cells may disappear temporarily but usually persist, as do the renal lesions, as evidenced by persistent microscopic hematuria and cast formation. It is generally felt that cures rarely if ever occur, but all agree that a significant prolongation of life in lupus erythematosus can be obtained. The development of a nephrotic syndrome, with anasarca, heavy albuminuria, hypoalbuminemia, hypercholesterolemia and, finally, progressive azotemia and death, is occurring with increasing frequency in the experience of our clinic, and this presents a difficult problem in management.

Haserick's [12] contribution toward improved management of this disease, especially in acute lupus crisis, is worthy of note. During crisis he has given massive doses of cortisone, up to 2,300 mg. in 24 hours, with favorable results. The analogy between adrenal steroid requirements in lupus crisis and insulin requirements in diabetic coma is a very apt one, and the use of large doses has improved the over-all results in this disease entity. Rigorous antibiotic therapy during crisis is important, since infection may play a role in its onset. A very definite step forward in the management of this previously uncontrollable disease has been made in the past five years, but many problems are still unanswered.

In *scleroderma* a transient moderate clinical improvement during ACTH or cortisone administration appears to be the extent to which either exerts a beneficial effect.

In *dermatomyositis* these hormonal agents have caused varying degrees of improvement up to what is considered a complete clinical remission, confirmed by the disappearance of cellular infiltration in the interfibrillar spaces and reduction in interstitial edema. Only in the early acute stages, before fixed tissue changes occur, can remission be expected to take place.

The only renal disease in which ACTH and the adrenal steroids have been beneficial is the *nephrotic syndrome*. Any individual who has observed the diuresis which may occur during or following the administration of these hormones can only agree that the response is dramatic. No agreement as to the number and the permanency of the remissions which are seen exists. Adults as a whole show only very temporary improvement, which is most apt to be noted in conjunction with the diuresis and loss of edema follow-

ing therapy. With the diuresis in children there is a decrease or disappearance in albuminuria, a fall in the serum cholesterol and a return of the plasma proteins toward normal levels.

In diseases of the gastrointestinal tract the favorable use of the hormonal agents has been confined to ulcerative colitis and some cases of steatorrhea. In regional enteritis, infectious hepatitis and cirrhosis there is no agreement as to whether benefit ensues following their use. We feel that the effects in hepatic disease are nonspecific, and that in chronic liver disease with borderline cholemia, hepatic coma and death may be precipitated.

Since the initial favorable response of *ulcerative colitis* to ACTH administration reported by Du Toit and Bauer,[13] many conflicting reports of the value of these agents in this disease have appeared. In a disease affected by such a diversity of psychiatric stimuli, and one in which spontaneous remissions and exacerbations are known to occur, evaluation of any therapeutic agent is difficult. In most patients we have observed prompt remission of symptoms, characterized by a marked decrease in diarrhea, disappearance or diminution of blood in the stools, improvement in the appearance of the mucosa, relief of abdominal pain, fall in temperature and an increased appetite. This is particularly so in the early cases, where our longest remission has been 60 months. In our experience, therapy must be of long duration for the best results, and it should be emphasized that when extensive fibrosis and cicatrization are present no response to hormone administration should be anticipated.

These views have been supported by the recent extensive reports by Kirsner and Palmer,[14] and particularly by the Joint Trials Committee of the Medical Research Council of Great Britain.[15] They conclude that these agents exert a beneficial influence on the outcome of an acute attack of ulcerative colitis, particularly when this is a first attack. This new and valuable adjunct in the management of ulcerative colitis should not be used to the exclusion of the well recognized general supportive measures.

The use of ACTH and cortisone in acute and chronic respiratory disorders is largely concerned with their possible role in infection. In certain chronic pulmonary disorders characterized by fibrosis, such as *beryllium granulomatosis,* corticotrophin and the adrenal cortical steroids have been beneficial, as manifested by a decrease in sputum and exertional dyspnea and a disappearance of pulmonary râles. The vital capacity and the maximal breathing capacity return toward or to the predicted normal levels, and there is x-ray evidence of clearing of the pulmonary lesions.

Some patients with pulmonary and other forms of *Boeck's sarcoid* have been benefited by the adrenal cortical steroids, especially when the lesions are of the early exudative type. Advanced lesions usually fail to respond.

Only brief mention of the effects of these hormonal agents in neurologic, hematologic, neoplastic, ophthalmologic and dermatologic disorders will

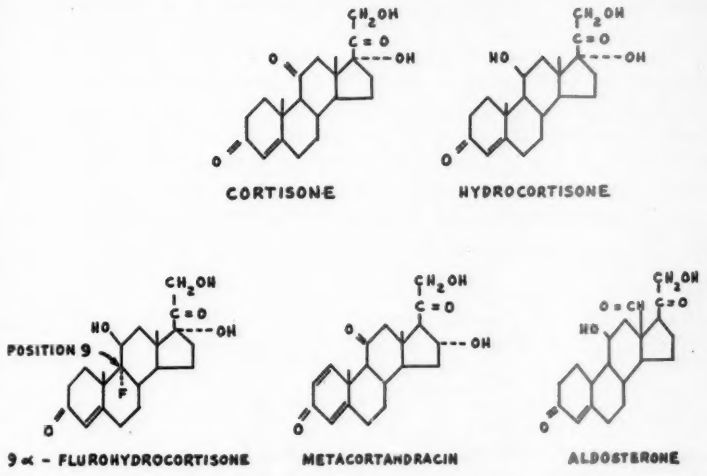

FIG. 3. Structural formulae showing the close relationship of cortisone and hydrocortisone to the newer synthetic analogues.

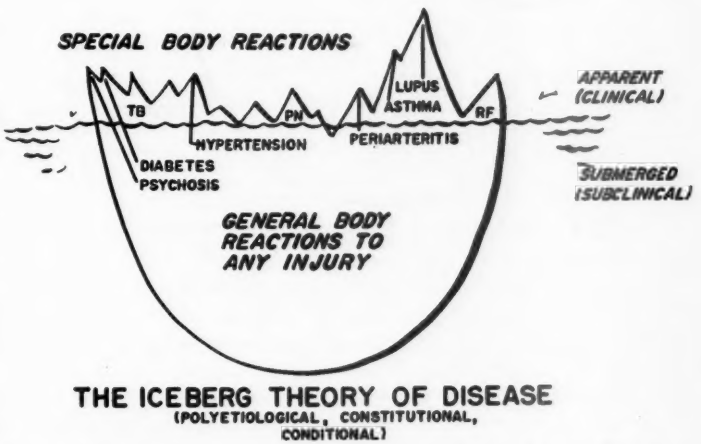

FIG. 4. Schematic representation of the "iceberg theory" of disease. Note the peaks of the iceberg represent the symptoms and signs of a disease, while the submerged portion represents the general body reaction to any injury.*

*We wish to thank Dr. John L. Bakke, Veterans Administration Hospital, Seattle, Washington, for the following schematic drawings.

be made because of my limited experience in these fields. The treatment of central nervous system, neuromuscular, neurotic and psychotic disorders has on the whole been disappointing. Hormone therapy leads to elation, optimism and an increase in the tempo of thinking and physical activity. Personality conflicts in psychologically inadequate patients become more marked, resulting in mild hypomania, depression, or both. We feel that the psychologic changes which occur during hormone administration are a release and exaggeration of premorbid personality trends.

In the neoplastic and hematologic disorders, the adrenal cortical steroids may lead to temporary remissions in acute leukemias, lymphosarcoma, chronic lymphatic leukemia, Hodgkin's disease and multiple myeloma. They tend to minimize the side effects of nitrogen mustard. Cortisone alone and combined with nitrogen mustard has led to favorable—although usually short-lived—responses in metastatic carcinoma of the breast.

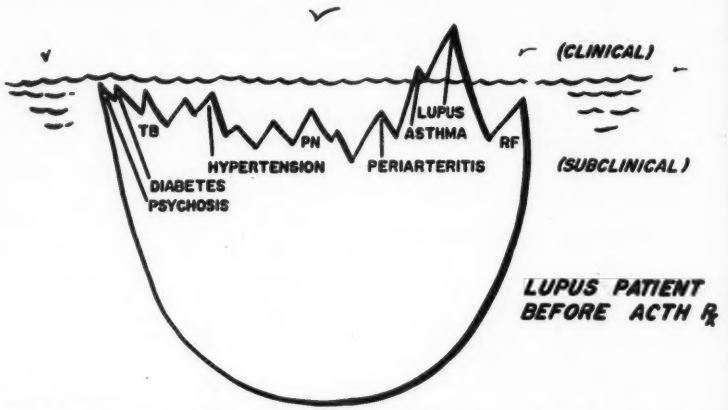

FIG. 5. Schematic representation of the findings in a patient with lupus erythematosus before treatment.

An important use has been found in the acquired hemolytic anemias, including those secondary to the lymphomas and the leukemias. In agranulocytosis these agents stimulate white cell production and have simplified the management of this disorder.

In ophthalmic therapeutics the action of the hormonal agents is limited to the control of inflammation and exudation. They have no direct antibiotic or chemotherapeutic action, and act on the reactivity of the tissues to the particular irritant.

Topical cortisone is ineffective in skin diseases, but topical hydrocortisone is most useful. It is highly effective in the lesions of atopic dermatitis, in contact dermatitis, and in pruritus ani and pruritus vulvae. Systemic use of these agents in pemphigus and exfoliative dermatitis has been life-saving.

The most significant progress in the last year may have been in the development of new synthetic analogues of cortisone and hydrocortisone (figure 3). All four 9α-halogen derivatives of cortisone and hydrocortisone have been found to have various activities similar to the physiologically occurring adrenal cortical steroids. Our experience with 9α-fluorohydrocortisone acetate has shown it to have profound effects on electrolyte and water metabolism. This has limited its clinical use in diseases other than adrenal insufficiency. The newest development, metacortandracin (Δ-1 cortisone), has been reported by Bunim [16] to be markedly antirheumatic at a dose level where the other physiologic effects of the adrenal steroids are minimal. Thus the decisive relationship between chemical structure, physio-

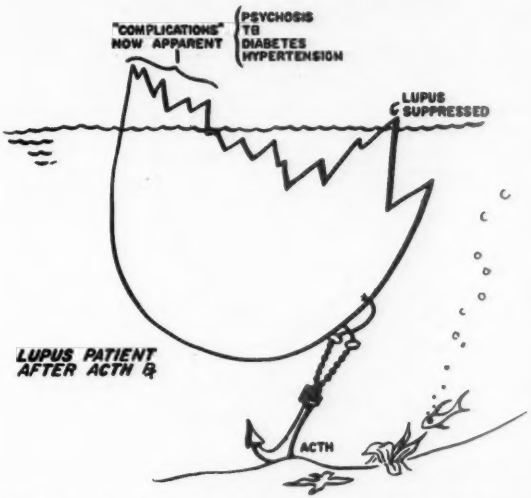

FIG. 6. ACTH has altered or "melted away" a part of the submerged portion—i.e. has modified the organism's response to a disease, with the production of side effects of ACTH therapy.

logic function and clinical effect has been reëmphasized, and it seems likely that new synthetic analogues may arise with marked anti-inflammatory activity and little if any action on water, electrolyte balance and intermediary metabolism of carbohydrates, fats and proteins.

An attempt has been made to give a panoramic view of the present use of ACTH and the adrenal steroids in only a proportion of the diseases in which they are used today. Although a vast number of clinical observations on the effects of these hormonal agents have been made, there is as yet little or no insight into the mechanisms by which these effects are produced and their site of action. It is postulated that there must be some fundamental action on cellular metabolism, which may lead to an alteration in the

mechanism of response of the cells to the many unknown factors which lead to disease. Browne's philosophic concept of the "iceberg" theory of disease is a useful one (figures 4, 5, 6, 7): that, like the iceberg, many of the organism's responses to disease are similar and submerged below the surface; that the symptoms and signs which we recognize as disease entities are the visible peaks of the iceberg; and that the adrenal cortical hormones tend to alter or "melt away" the submerged portion, causing the visible peak, which is recognized as a disease, to disappear below the surface. As our observations increase we are repeatedly struck by the evidence of progression of the disease in spite of clinical remission. This is particularly true in the mesenchymal diseases, such as rheumatoid arthritis, rheumatic fever and

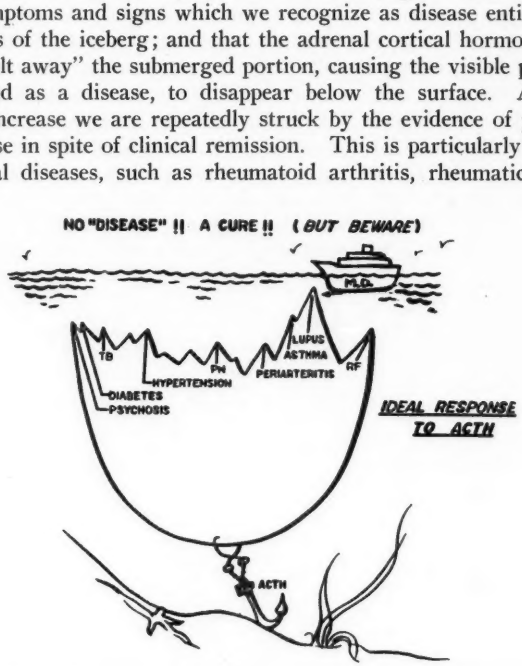

FIG. 7. Schematic representation of the ideal response to ACTH or adrenal steroid therapy.

lupus. This progression suggests that one "deviates" the disease but does not alter its basic course.

One of the most significant contributions of these agents has been in demonstrating the potential reversibility of complex disease, which should stimulate further inquiry into their pathogenesis with the hope of an ultimate understanding.

SUMMARIO IN INTERLINGUA

Le valor clinico-medical de ACTH e del steroides adrenal es plus firmemente establite, sed le rolo definitive de iste agentes in le arsenal therapeutic se trova ancora sub crystallisation. Es sublineate le importantia del comprehension de lor effectos physiologic como precondition de lor non-riscose e efficace uso therapeutic. Le inhibition endogene del ACTH pituitari, le qual occurre in consequentia del administration de ACTH exogene, e le atrophia adrenocortical, le qual accompania le administration

de cortisona e hydrocortisona (specialmente in casos de prolongate therapias con iste agentes), pote producer un insufficientia adrenal temporari post le cessation del therapia. Es discutite le typos de agentes hormonal in uso currente e le dosages e horarios de lor administration. Cortisona e hydrocortisona ha rendite possibile therapias a reimplaciamento in casos de morbo de Addison e de hypopituitarismo, restabliente le patientes a un stato de valetude multo proxime al norma. Es describite le uso del nove steroide synthetic, 9-alpha-fluorohydrocortisona, tanto per se como etiam in combination con hydrocortisona, in le tractamento de morbo de Addison.

Es discutite le effectos benefic de ACTH, cortisona, e hydrocortisona in arthritis rheumatoide, gutta, febre rheumatic, asthma bronchial, sensibilitates medicamentose, periarteritis nodose, disseminate lupus erythematose, nephrosis, colitis ulcerative, granulomatosis a beryllium, e lupus pernio. Es sublineate le exhortation que le agentes hormonal non deberea esser usate al exclusion del altere ben-recognoscite formas de therapia in iste morbos.

Le plus significative progresso durante le anno passate esseva le elaboration de nove synthetic analogos de cortisona e hydrocortisona. Metacortandracina se trova in extense usos experimental, e nos debe considerar le possibilitate que on discoperira un analogo con un forte efficacia anti-inflammatori e paucos o nulles del negative effectos lateral que es characteristic del agentes hormonal.

Nos non sape multo in re le mechanismos per que iste agentes hormonal produce lor effectos o in re le sito de lor action. Es postulate que illos debe exercer qualcunque effecto fundamental super le metabolismo cellular e que isto resulta in un alteration del responsa del cellulas al agentes etiologic que causa le morbo. Le uso de ACTH e del steroides adrenal ha demonstrate le reversibilitate potential de certe morbos. On pote supponer que recercas in re lor pathogenese va esser stimulate per iste facto.

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ADRENOCORTICOTROPIC HORMONE AND ADRENAL STEROIDS IN THE MANAGEMENT OF INFECTIOUS DISEASES *

By Wesley W. Spink, M.D., F.A.C.P., *Minneapolis, Minnesota*

In their initial reports upon the effects of corticotropin and cortisone in patients having rheumatoid arthritis or rheumatic fever, Hench and his associates [1, 2] emphasized two manifestations: inflammation of the tissues was subdued, and the patients experienced a remarkable sense of well-being. Soon thereafter, extensive observations were made by others [3, 4, 5] in human subjects having a variety of infections, and in experimentally infected animals. It was demonstrated in patients with pneumococcal pneumonia that the administration of ACTH caused a crisis and striking improvement, although pneumococci persisted in the tissues for many days.[6] On the other hand, it was also shown in many species of animals infected with different types of microörganisms that administered hormones would rapidly convert a mild infection into a fulminating and lethal disease. Likewise in man, the use of steroids was complicated by the appearance of infection, including the activation of latent tuberculosis. These early observations introduced a fortunate note of caution into the indiscriminate application of these agents to the management of infectious diseases. Although much more basic information is urgently needed, accumulated experience now justifies the careful employment of ACTH and the corticosteroids in selected patients with infectious diseases. Not only will these hormones alter the course of the disease favorably for patients, but also at times lives can be saved.

Although it is not established at present what mechanism or mechanisms are involved in the protection against infection afforded to patients by these hormones, it has been appreciated by clinicians for many years that in the presence of adrenal insufficiency patients have a very brittle defense mechanism against bacterial diseases. Streptococcal pharyngitis in patients with Addison's disease proved to be a terrifying and devastating infection on many occasions. Though the precise pathologic physiology embraced in the Waterhouse-Friderichsen syndrome is disputed, there is little doubt that adrenal insufficiency does participate in the picture of shock. Extended observations in patients critically ill with many types of infection do indicate that varying degrees of adrenal insufficiency are not at all uncommon.

The purpose of this presentation is to point out the desirability of the short-term use of corticotropin or corticosteroids in critically ill patients

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having certain infectious diseases with and without serious complications. The discussion will revolve around three aspects of the problem that have been of interest to the groups at the University of Minnesota. First, consideration will be given to some of the indications for the use of the hormones when it is desirable to allay the inflammatory response to infection or to eliminate a severe toxic state. Second, there is evidence that the administration of the steroids, along with appropriate antimicrobial therapy and pressor agents, contributes to the recovery of patients who have suffered peripheral vascular collapse and shock due to an infectious agent. Third, an ever-increasing number of patients are developing serious hypersensitivity reactions to therapeutic agents used in infectious diseases, and the prompt administration of the steroids will subdue these harmful reactions.

Some Indications for Employing the Steroids for Combating the Toxemia of Infectious Diseases or Inflammatory Complications

It is not possible to present at this time a comprehensive review of all the indications for the use of corticotropin or the corticosteroids in infectious diseases; therefore, emphasis will be placed upon a selected group of diseases, and upon some of their complications. When a steroid is employed in the management of an infectious disease, except in occasional instances, it is highly desirable to protect the patients with antimicrobial agents, since the hormones do reduce the efficiency of the defense mechanism against microörganisms.

Tuberculosis: The effectiveness of antituberculosis drugs in the management of this disease and its complications suggests in itself that there are but few indications for employing the steroids.[7] Since the hormones do subdue the inflammatory response to tuberculin, they may be offered to patients under selected circumstances, but always along with antituberculosis agents. These indications include critically ill patients having a rapidly advancing inflammatory lesion, as in tuberculous pneumonia, or in persons having ocular tuberculosis. Treatment of tuberculosis in some individuals is handicapped by the appearance of hypersensitivity to the antituberculosis drugs, and hormone therapy may be successfully combined with these drugs, thus preventing the manifestations of hypersensitivity.[8] An undesirable complication of tuberculous meningitis is the inflammatory reaction of the subarachnoid space that can block the canal, or that can cause a walling off of tubercle bacilli, so that a relapse may ensue. Some investigators [9, 10] have reported that the steroids used in combination with the antituberculosis drugs will allay the inflammatory response in meningitis and speed up permanent recovery.

Acute Rheumatic Fever: There is no question that ACTH or the corticosteroids can suppress the generalized inflammatory reaction in the acute phase of rheumatic fever.[11] There is some doubt whether the hormones will

prevent ultimate endocardial damage to a greater extent than will rest and salicylates, although a few investigators favor the steroids over salicylate therapy.[12] The recent joint report of the coöperative groups from the United Kingdom and the United States stated that no difference in the incidence of endocardial lesions was noted at the end of a year in patients treated with salicylates or with corticosteroids.[13] Up to the present time we have elected to use ACTH or the corticosteroids only in critically ill patients with acute rheumatic fever, and always in conjunction with salicylates and penicillin. The advantages gained in treating a critically ill patient with ACTH are noted in the following case.

Case Report

Case 1. A 21 year old college student was admitted to the hospital critically ill with a severe sore throat, pain in the left side of the chest, and nausea and vomit-

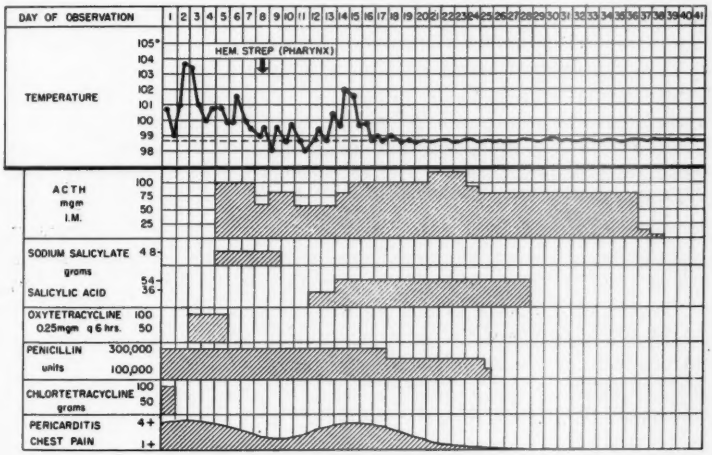

Fig. 1. Patient with severe rheumatic pericarditis following acute streptococcal pharyngitis responding favorably to ACTH. Note relapse of pericarditis when dose of ACTH was reduced.

ing. The essential features on examination included an exudative pharyngitis of hemolytic streptococcal origin, cervical adenitis, consolidation of the left lower lobe, and a to-and-fro pericardial friction rub. He was cyanotic and complaining of severe chest pain. His clinical course is depicted in figure 1. In view of the debilitating pleural and pericardial reaction, and the critical nature of his illness, ACTH was administered on the fifth hospital day, along with salicylates and penicillin. At this time a gallop rhythm was present, and he was expectorating bloody sputum. He was given 25 mg. of ACTH intramuscularly every six hours. By the following day he was considerably improved. The friction rub was inaudible, but his pharyngitis was still severe. When an attempt was made to reduce the dose of ACTH his condition worsened. It was necessary to continue ACTH for a total of

34 days. Therapy with salicylates had to be omitted because of nausea and vomiting. He recovered completely, with no residual cardiac complications appearing in the following five years.

In the foregoing case the prompt administration of ACTH tided this patient over a very critical period in his illness.

Typhoid Fever, Brucellosis, and the Rickettsial Diseases: These diseases may be considered together, since they represent infections in which intracellular parasitism is a prominent feature, and in recent years the antibiotics have revolutionized the management of these human afflictions. ACTH or the corticosteroids are indicated in the therapy of selected cases of typhoid fever, always simultaneously with the administration of chloramphenicol. There are two reasons for utilizing the hormones in this disease. First, toxemia can be very severe, and even after the administration of chloramphenicol this manifestation will persist for several days. And second, sometimes in a critically ill patient the initial dose of chloramphenicol may be followed in a few hours by an accentuation of the symptoms, a further rise in temperature, and even the appearance of shock. This is presumed to be due to the antibiotic's acting as a bacteriostatic agent against the typhoid organisms, and with death of the bacilli, somatic antigen or endotoxin is liberated. It has been presumed in both typhoid fever and brucellosis that the surface antigen of the bacterial cell, consisting of a lipoprotein-carbohydrate complex, is at least partly responsible for the pathogenesis of the two diseases.[14-16] When a steroid is administered simultaneously with chloramphenicol in typhoid fever, improvement of the patient occurs much more rapidly than when chloramphenicol is used alone.[17] Hormone administration need not be continued for more than 48 to 72 hours. Likewise, patients seriously ill with brucellosis will improve more rapidly than when only antibiotics are given. The results with ACTH in brucellosis have been detailed elsewhere.[18] The steroids are not indicated in indolent and prolonged states of chronic brucellosis. The treatment of an acute attack of brucellosis is illustrated by the following:

Case 2. A 36 year old white male employee of a meat-packing plant had been very ill for one week with chills, fever, severe weakness, nausea and anorexia. His temperature was 104.4° F.; pulse, 100. Splenomegaly was detected. Brucella agglutinins were present in a titer of 1 to 5,120, and *Brucella abortus* was isolated from the blood. Initially he was given 20 mg. of ACTH in an intravenous infusion for two succeeding days, and then 20 mg. in gel twice daily intramuscularly for four more days. Simultaneously, dihydrostreptomycin was administered intramuscularly in a dose of 1 gm. twice daily for one week, and then 0.5 gm. twice a day for a second week. Tetracycline was taken orally in a dose of 0.5 gm. four times daily for three weeks. Under this régime he improved rapidly, and he has remained well for over a year.

The foregoing therapy for severe brucellosis has been modified slightly in that hydrocortisone is employed instead of ACTH, in a single dose of 100 mg. administered intravenously in an infusion of 500 ml. of 5% glucose

and water. Then during the succeeding 24 to 48 hours, hydrocortisone is given orally in a dose of 25 mg. four times daily. When the hormone is used in severe cases of brucellosis dramatic improvement occurs within 18 to 24 hours, whereas with antibiotics alone the toxemia and anorexia do not abate for four to five days.

The remarkable improvement obtained so rapidly with the tetracycline drugs and chloramphenicol in the rickettsioses, such as Rocky Mountain spotted fever, epidemic typhus and scrub typhus, necessitates the use of the steroids only on occasion. It should be emphasized that desperately ill patients seen late in the course of the disease may not respond to antibiotic therapy, and in such instances hormone administration can be of considerable value.[19]

Trichinosis: This parasitic disease is manifested chiefly by diarrhea, myositis, and the serious complications of encephalitis and myocarditis.

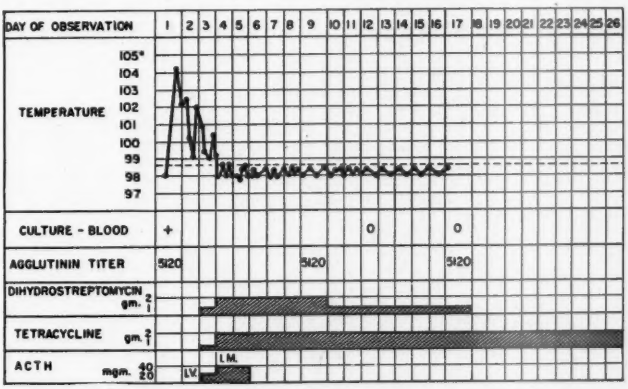

FIG. 2. Clinical course of patient with acute brucellosis. A prompt reduction in fever and diminution of toxemia took place following the administration of ACTH. Note that antibiotics were given simultaneously.

Until ACTH and corticosteroids became available there were no agents for interrupting the course of this disease, but several reports have attested to the value of the steroids in trichinosis.[20-28] The following case, under the care of Dr. Robert Wise, demonstrates a dramatic response to steroid therapy in a patient seriously ill with trichinosis.

Case 3. A 42 year old housewife had been acutely ill for one week with nausea, vomiting and diarrhea, and daily spikes of fever. The patient appeared quite weak and lethargic. During the first five days in the hospital her temperature spiked up to 104° F. daily, and the correct nature of her disease was suspected when she complained of pain in her muscles on the fifth day, and an eosinophil count of 13% was detected (figure 3). A biopsy of the gastrocnemius muscle showed the presence of *Trichinella spiralis* (figure 4). She was then given 100 mg. of hydrocortisone in an infusion, which was followed by a daily oral dose of 200 mg. of cortisone.

It was necessary to continue the cortisone therapy in diminishing doses for 16 days. A second biopsy of the gastrocnemius muscle obtained after the completion of therapy showed encystment of the parasite progressing in a manner similar to that in cases that had not been offered hormones (figure 5). She recovered, but one week later an enteritis due to *Salmonella newport* occurred, which responded to treatment with chloramphenicol.

The foregoing patient was critically ill. She was dehydrated and exhausted. Following the initial infusion of hydrocortisone she experienced prompt improvement and the anorexia subsided.

Viral Diseases: The treatment of hepatitis of viral origin with the corticosteroids, has been the subject of considerable investigation and favorable results have been recorded.[24] In an extensive series of observations by

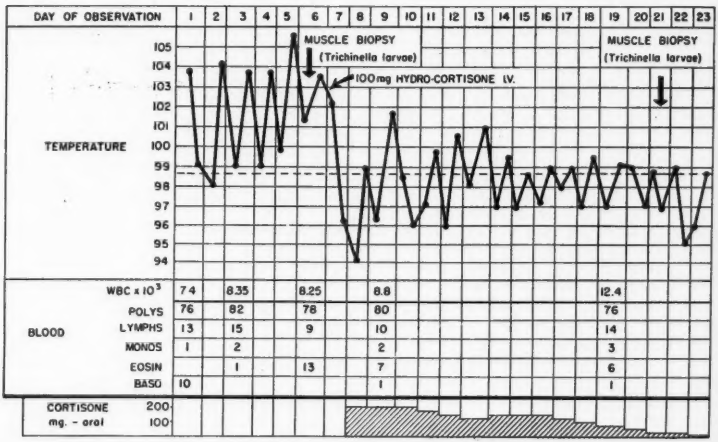

FIG. 3. Patient acutely ill with trichinosis, showing prompt drop in temperature following start of adrenocorticosteroid therapy. Note febrile relapse when dose of cortisone was reduced.

Evans and his associates,[25] both ACTH and cortisone appeared to speed up recovery in the acute cases, but relapses of the disease occurred more frequently in the treated patients than in the control group of untreated cases. We have not observed consistent improvement in patients treated with the steroids, and employ these hormones only in the more severe cases. Under these circumstances, prompt improvement has been noted in an occasional patient.

Orchitis is a painful and incapacitating complication of mumps. Unilateral testicular atrophy occurs occasionally. Treatment of acute orchitis including therapy with estrogenic hormones, such as stilbestrol, has not been too satisfactory. Prompt improvement with the subsidence of inflammation has occurred following the administration of corticotropin or cortisone.[26, 27]

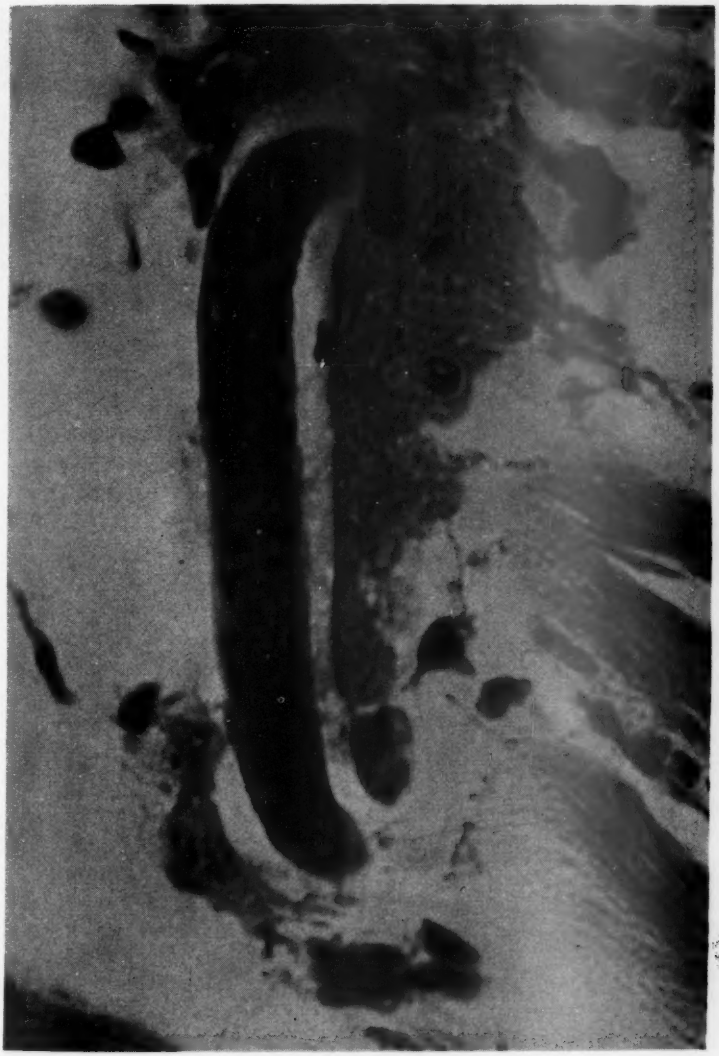

FIG. 4. Showing larva of *Trichinella spiralis* in specimen of gastrocnemius muscle removed from acutely ill patient (figure 3) just before administration of hydrocortisone.

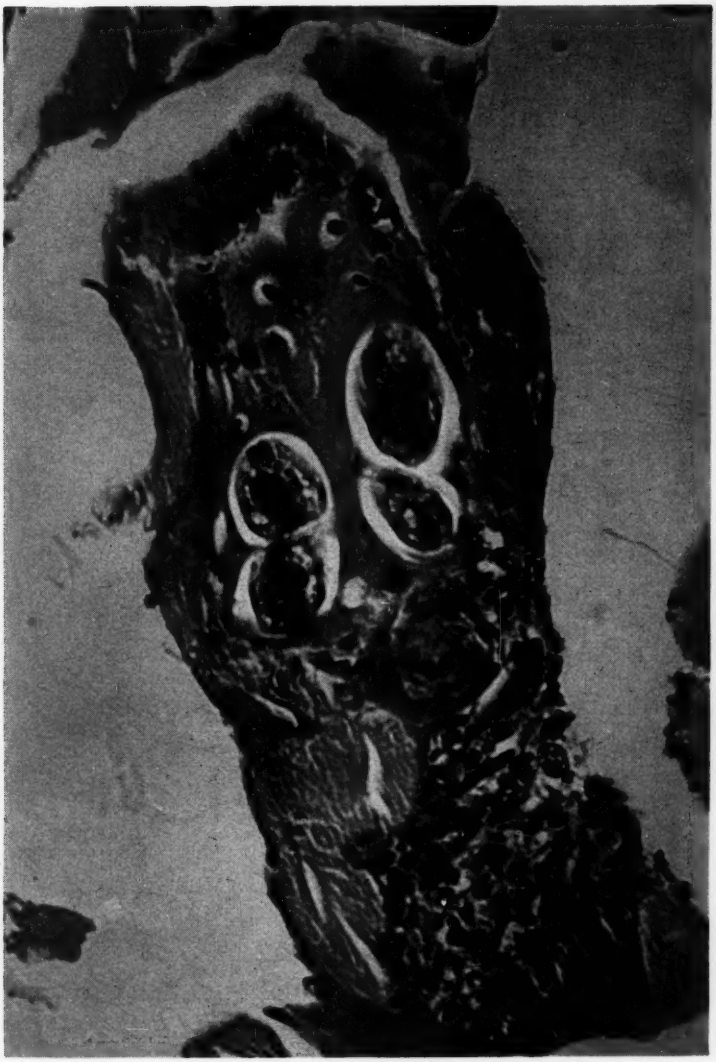

FIG. 5. Larva of *Trichinella spiralis* in specimen of gastrocnemius muscle excised after cortisone had been administered for two weeks (figure 3). Note that encystment is progressing normally. There is still evidence of inflammation.

Infectious mononucleosis remains undefined etiologically. A virus is probably the responsible agent. Complications may be serious, and include encephalomeningitis, myocarditis, hepatitis and rupture of the spleen. Satisfactory therapeutic agent or agents have been lacking. Prompt and dramatic improvement has followed the administration of corticotropin, as was demonstrated in the following critically ill patient, who was treated by Dr. Wendell Hall:

Case 4. A 21 year old white male had been ill for two weeks with a severe headache, abdominal pain, weakness, prostration, anorexia and vomiting. He had lost 15 pounds in weight. His temperature reached 105° F. daily. On admission to the hospital he appeared quite ill. His temperature was 104° F. (figure 6). He

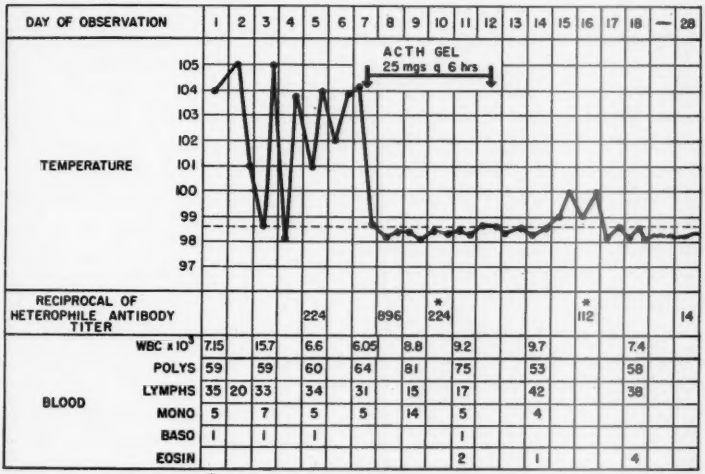

FIG. 6. Patient seriously ill with infectious mononucleosis responding promptly to ACTH. Note that heterophil antibody persists in the blood during therapy. Also note the reduction in lymphocytes as a result of ACTH.

had generalized adenopathy, splenomegaly and hepatomegaly. His total leukocyte count was 7,150, with 35% lymphocytes, many of which were atypical. The heterophil antibody titer was 1 to 224. After having been under observation for one week his condition failed to improve and he was given 25 mg. of ACTH gel intramuscularly every six hours for 5 days. This was associated with prompt improvement. The adenopathy receded, and the spleen and liver diminished in size. It is to be noted that, coincident with the administration of ACTH, the number of lymphocytes decreased but reappeared after the administration of ACTH was discontinued. Heterophil antibody persisted in the serum during and after ACTH therapy. There was no relapse after the hormone was withdrawn.

An instance of "cat scratch fever" with thrombocytopenic purpura has been reported to have responded to steroid therapy.[28] The hormones do not favorably influence the course of poliomyelitis.

Therapeutic Evaluations of the Steroids in Infections Associated with Shock

Peripheral vascular collapse is an occasional accompaniment of bacteremic states, occurring especially in infections due to gram-negative organisms. The collapse is in part related to the presence of bacterial endotoxins. Adrenal insufficiency is only one aspect of an expression of complicated abnormal physiology. Although Ebert and Stead [29] found the blood volume to be normal in these cases, others [30] have suggested that the blood volume is reduced in proportion to the total vascular capacity induced by the vasodilatation and peripheral pooling of blood. It has been shown experimentally that the appearance of shock coincides with a reduced cardiac output. We have obtained experimental and clinical evidence that the corticosteroids will prevent the appearance of shock, and there are indications that the hormones will aid in the reversal of shock during the early stages.

The Waterhouse-Friderichsen Syndrome: This syndrome is generally interpreted as peripheral vascular collapse occurring in young patients having an acute and fulminating illness due to meningococcal meningitis and bacteremia, with the primary cause of shock being ascribed to adrenal insufficiency. This concept is inadequate in the light of many well studied cases. Other microörganisms can be responsible for the primary infection, and adrenal insufficiency has not always been the major factor in precipitating the collapse, but it has been a contributing determinant in many cases. Prompt therapeutic action is necessary in the management of this syndrome. Sulfadiazine, with or without penicillin, should be given for meningococcal infections. A favorable outcome has been reported following the additional use of corticosteroids.[31-33] Others [34, 35] have employed a pressor agent, such as l-norepinephrine, with anti-meningococcal therapy, and often with cortisone. Kinsell [36] has advocated the use of corticotropin and corticosteroids, along with sulfadiazine, for every case of meningococcal meningitis as a prophylactic procedure against the appearance of vascular collapse. The Waterhouse-Friderichsen syndrome in meningococcal sepsis presents a desperate situation, and we would also advocate the prompt use of a pressor agent with corticosteroid administration and sulfadiazine.

Shock Due to a Variety of Gram-Negative Bacilli: Many different species of gram-negative bacteria of low virulence reside in the human intestinal tract. When these microbes gain entrance into the blood stream of man irreversible peripheral vascular collapse may occur, due to the endotoxin liberated from the organisms. This sequence of events has been produced by such species as *Escherichia coli, Aerobacter aerogenes, Pseudomonas aeruginosa,* proteus species, the paracolon group and others.[37] These bacteria can be introduced into the blood stream with disastrous results following a transfusion of contaminated blood.[38, 39] Obstruction along the urinary tract with localized infection, followed by invasion of the blood stream, is

a frequent cause of collapse. Infection of the biliary tract may give rise to a bacteremic state and collapse.

We have been carrying out experimental and clinical studies in an attempt to define the pathogenesis of the shock that is induced by these bacterial endotoxins, and several therapeutic procedures have been evaluated. In the present discussion brief attention will be given to the prevention and treatment of the peripheral vascular collapse. Initial observations with Waisbren [37] revealed that shock could be prevented, or the collapse occurring during the early stages could be satisfactorily managed, with properly selected antibiotics. The tetracycline agents proved to be effective against the coliform group of bacteria. Subsequently, in some cases it was observed that the shock progressed regardless of antibiotic therapy, and a pressor

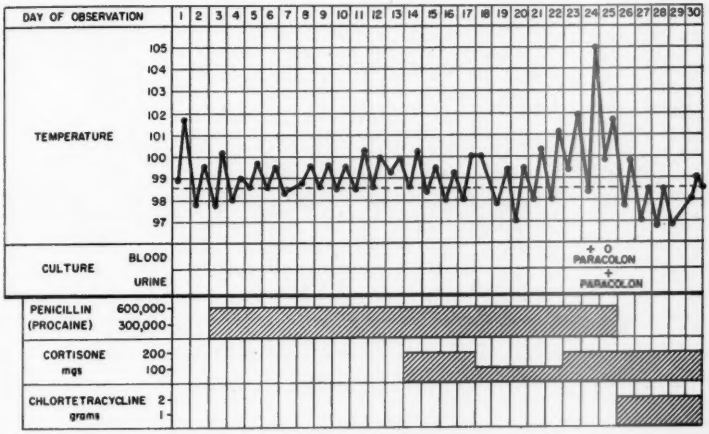

FIG. 7. Patient with myelogenous leukemia. Cortisone was administered for hemolytic anemia. It is predicated that cortisone prevented serious deterioration of the patient when blood stream was invaded by paracolon organisms. Bacteremia controlled with chlortetracycline.

agent, such as 1-norepinephrine, was found to be beneficial.[40] Additional observations indicated that adrenal insufficiency participated in the collapse, and the administration of corticosteroids appeared to be beneficial in instances of impending shock, as well as in cases of peripheral vascular failure. This was in accord with the observations of others.[41] There is evidence that corticotropin and the corticosteroids potentiate the action of 1-norepinephrine.[42]

The advantages of employing corticosteroids along with a pressor agent and antibiotics in the prevention and treatment of shock due to bacterial infections are illustrated in the following cases. The first case to be cited is of interest because it represents a patient who was seriously ill, and the

administration of cortisone possibly prevented a state of vascular collapse when the blood stream was invaded by a paracolon bacillus.

Case 5. A 30 year old white male was seen with Dr. Wendell Hall. He had been admitted to the hospital in a state of weakness, and was found to have acute myelogenous leukemia and hemolytic anemia. To combat the hemolyzing process, cortisone was administered orally in a dose of 50 mg. four times daily. As a prophylactic measure he was given penicillin. During the course of his illness a paracolon bacillus appeared in his urine and in his blood (figure 7). He was febrile, but vascular collapse did not occur. The paracolon bacillus was refractory to the antibacterial action of penicillin but sensitive in vitro to chlortetracycline. The prompt administration of this agent along with the cortisone eradicated the infection.

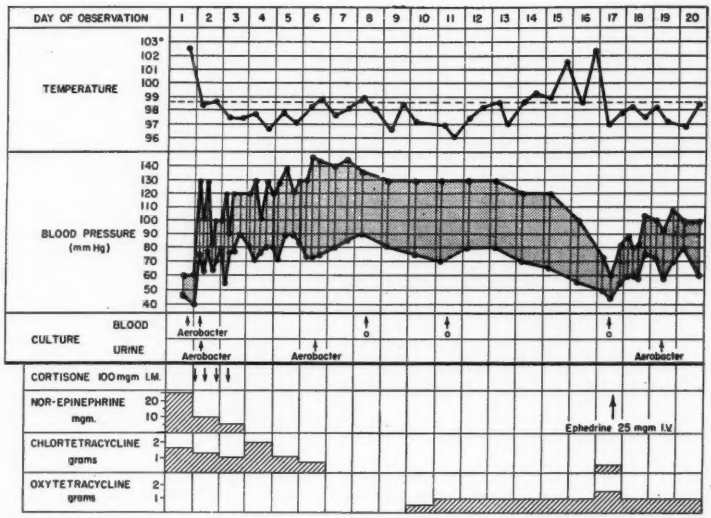

FIG. 8. Elderly male who had prostatic obstruction and, following catheterization, bacteremia due to *Aerobacter aerogenes* occurred and shock followed. Cortisone, norepinephrine and tetracycline drugs administered simultaneously with improvement.

Previous clinical experience with blood stream invasion by paracolon bacilli had shown that this microörganism would cause vascular collapse. The foregoing patient with acute leukemia probably possessed a fragile defense mechanism to start with, and if cortisone had not been offered to the patient prior to his infection it is not unlikely that shock might have ensued. The cortisone did provide a paradoxic situation in that the steroid probably contributed to a rupture of his defense mechanism so that invasion of the blood stream did occur, but at the same time the sequence of events following adrenal insufficiency was possibly prevented.

A second case demonstrates a clinical picture that is seen not uncommonly.

Case 5. An 86 year old white male had been disturbed for some time by urinary retention caused by prostatic obstruction. Several hours prior to his entry into the hospital a catheter had been introduced into his bladder. He developed chills and fever and when first seen was in shock (figure 8). A constant, intravenous infusion of 1-norepinephrine was instituted and continued for 60 hours. He was given chlortetracycline and 400 mg. of cortisone intramuscularly over a period of 24 hours. It is to be noted that *A. aerogenes* was cultured from his blood stream and from his urine. He recovered and remained well, except that several days after admission he became febrile while receiving antibiotic therapy. There was a mild drop in blood pressure, which appeared to respond to ephedrine given intravenously. It is of interest that six months later a transurethral prostatic resection was carried out, and he again developed shock, but he responded to treatment with a pressor drug, antibiotics and corticosteroid.

In a continuation of similar investigations with Dr. Max Weil and Dr. Robert Abernathy, an endeavor has been made to seek out a more desirable vasopressor agent than 1-norepinephrine, which must be given very cautiously by the intravenous route, so that constant attention by nursing personnel is essential. In some instances 1-norepinephrine has had to be given for many days, which involves considerable expense. In addition, if the drug escapes from the vein into the tissues severe necrosis ensues. Preliminary results with another synthetic vasopressor amine (Metaraminol) have been more satisfactory in that this material can be administered intermittently by the subcutaneous and intramuscular routes, thus obviating two undesirable features: the need for constant attention, and the danger of tissue necrosis.

ACTH and the Corticosteroids in the Management of Hypersensitivity States Induced by Drugs

Medicine has benefited greatly during the last few decades from the introduction of many drugs for the management of human diseases, including infections, but a disturbing aspect of this advancement has been the indiscriminate and promiscuous use of potentially dangerous compounds. An ever-increasing number of severe reactions is taking place on the basis of acquired hypersensitivity to many drugs, including the sulfonamides and the antibiotics. These reactions can be fatal. Fortunately, severe and debilitating illness induced by the drugs can be prevented and terminated by the prompt use of ACTH or corticosteroids.[43] Drug reactions include the immediate type, with fever and urticaria and at times, fatal anaphylactic shock. The delayed reactions simulating serum sickness include fever, skin eruptions, polyarthritis and polyarteritis. Another group of manifestations includes depression of the bone marrow with agranulocytosis, thrombocytopenia and purpura, and pancytopenia. Hemolytic anemia also occurs. The prompt recognition of these disorders and the immediate administration of the corticosteroids will induce dramatic improvement.

A serious complication of drug therapy is agranulocytosis, and corticotropin or cortisone has been valuable in correcting this marrow suppression.[44, 45] The following case illustrates a patient critically ill with agranu-

locytosis caused by amidopyrine. She was under the care of Dr. Boyd Thomes of Minneapolis.

Case 6. A 35 year old housewife developed a sore throat 48 hours before admission to the hospital. This became progressively worse, and severe chills and fever appeared. When admitted to the hospital she was quite ill. Her temperature was 103° F. There was a bilateral brawny induration, swelling and tenderness of the anterior cervical region. Swallowing was accomplished with considerable pain and difficulty. The pharynx was reddened and edematous, but no exudate was present. The total leukocyte count was 450, with 28 polymorphonuclear leukocytes and 72 lymphocytes. Although she received penicillin her condition deteriorated. On the second day her temperature was 105° F., and the total leukocyte count had dropped to 800 cells, with only 8 polymorphonuclear neutrophils being identified. She was then given 40 mg. of ACTH in gel intramuscularly, along with antibiotic therapy (figure 9). Coincident with this her condition improved dramatically, and

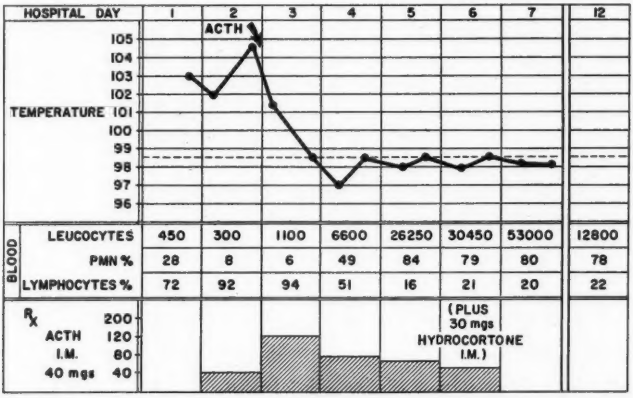

FIG. 9. Clinical course of patient with severe depression of granulocytes due to amidopyrine. Prompt improvement occurred following the administration of ACTH.

the total leukocyte count as well as the number of young granulocytes increased. Hormone therapy was continued for five days. On the seventh day her leukocyte count was 53,000, and then it gradually returned to normal.

DISCUSSION

A cardinal principle in human therapeutics is that no drug should be offered to any patient unless backed up by a reasonable degree of assurance that the agent will alter the clinical course favorably for the patient. The promiscuous and indiscriminate use of any drug is to be severely condemned. When one is confronted with a critically ill patient it may be necessary to administer an agent or agents that can elicit harmful side effects. Adrenocorticotropin and the corticosteroids have profound metabolic effects when administered to human subjects. The basic thesis of this presentation is that these hormonal agents, when given over a brief period of time to

critically ill patients with infectious diseases, or to those with debilitating complications as a result of infections, will often produce dramatic improvement without provoking harmful effects. In some instances the judicious and prompt use of these steroids can prevent fatalities.

Summary

1. Adrenocorticotropin and the corticosteroids subdue inflammation and suppress the toxicity in patients having infectious diseases. For these reasons these hormones are of value in carefully selected patients who are critically ill or who have debilitating complications.

2. Diseases in which the clinical courses have been favorably altered by the steroids include tuberculosis, acute rheumatic fever, typhoid fever, brucellosis, trichinosis, viral hepatitis, mumps orchitis and infectious mononucleosis.

3. Adrenal insufficiency may participate in the peripheral vascular collapse and shock that occur in bacteremic states, particularly in those caused by gram-negative bacteria. Adrenocorticosteroids may be used advantageously in such patients, along with antibiotics and pressor agents.

4. Severe hypersensitivity reactions, involving the skin, vessels, joints and bone marrow, which are induced by therapeutic agents, including the sulfonamides and antibiotics, can be promptly controlled by the administration of the corticosteroids.

5. It is emphasized that corticotropin and the corticosteroids have profound metabolic effects upon the human organism, and when used in the management of infectious diseases these agents should be given for only brief periods of time, and only to carefully selected patients.

Summario in Interlingua

Inspirate per le facto que ACTH e cortisona allevia le inflammation e reduce le grado de toxicitate in patientes con arthritis rheumatoide, nos ha executate un serie de observationes in patientes con differente morbos infectiose. Iste observationes esseva executate al clinicas affiliate con le Universitate Minnesota e coperiva un periodo de quatro annos. Le resultatos demonstra que le discriminante uso a breve durantia de ACTH e del adrenocorticosteroides in cautemente seligite casos produce frequentemente un marcate melioration.

Nos ha usate ACTH, cortisona, o hydrocortisona in tres gruppos de patientes. Primo, in un gruppo de patientes con morbos infectiose in que le suppression del inflammation e del toxemia esseva desirabile, le hormones esseva administrate como addendo al antibioticos. Le morbos includeva tuberculosis, acute febre rheumatic, brucellosis, febre typhoide, hepatitis, orchitis parotitic, mononucleosis infectiose, e trichinosis. Secundo, le hormones esseva usate—con e sin agentes pressorial e con antibioticos—in le therapia de choc inducite per bacteremia a micro-organismos gram-negative. Tertio, le hormones esseva usate in le tractamento de statos de hypersensibilitate causate per drogas, per exemplo anemia hemolytic e agranulocytosis.

Proque il es un facto que le adrenocorticosteroides ha negative effectos lateral e proque il pote occurrer que le mechanismo defensive contra micro-organismos es disfavorabilemente afficite per le hormones, iste agentes debe esser usate cautissimemente, durante brevissime periodos, e in casos de circumspectissime selection.

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THE RÔLE OF ACTH, CORTISONE AND HYDROCORTISONE IN SURGERY * †

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During the past few years a considerable amount of knowledge concerning the use and abuse of ACTH, cortisone and hydrocortisone in the treatment of surgical patients has accumulated. Metabolic alterations of varying magnitude and direction occur in the surgical patient in response to his disease or operation. Since the hormones under discussion are capable of producing significant metabolic changes, it is important to determine whether these are in a favorable or unfavorable direction. The purpose of this paper is to categorize the surgical patients in whom the use of ACTH, cortisone and hydrocortisone (a) is definitely indicated, (b) may be of benefit, or (c) is contraindicated.

It is a well documented fact that the adrenal gland secretes a broad spectrum of steroids which have a wide range of physiologic activity. Therefore, the effect of exogenous ACTH, which stimulates adrenal secretion, will be the sum of the effects of various fractions which are secreted. On the other hand, the administration of cortisone or hydrocortisone will result in the specific changes which these hormones are capable of producing. At the same time they may suppress the endogenous secretion of hormones mediated through the pituitary-adrenal axis. It is important to remember that the effects of ACTH, cortisone and hydrocortisone will be influenced by a number of existing factors (state of nutrition, age, sex, level of dietary intake, etc.).

To facilitate this discussion we have chosen to limit our remarks to the following fields:

I. The use of ACTH, cortisone and hydrocortisone as therapeutic agents.
   A. For the production of remissions and gaining of time for preparation of patients undergoing surgery (e.g., ulcerative colitis, hemolytic anemia, etc.).
   B. For the treatment of surgical disorders and complications (e.g., pancreatitis, tetanus, thrombophlebitis, thyroid crisis, etc.).
   C. For patients with adrenal insufficiency or inability to respond normally to stress because of prior ACTH or adrenal steroid therapy (e.g., patients with Addison's disease, those who have had adrenal-

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ectomy, individuals with Waterhouse-Friderichsen syndrome, and those who had suppression of the pituitary or adrenal glands because of previous endocrine therapy).

D. The rôle of endocrine therapy in shock and peritonitis.

E. Partial or total adrenalectomy.

1. For diseases of the adrenal gland per se (e.g., Cushing's or adrenogenital syndrome, pheochromocytoma or primary aldosteronism).
2. For diseases without primary adrenal gland involvement (e.g., palliation of metastatic carcinoma, hypertension or secondary aldosteronism).

II. Factors governing the metabolic response of the patient to stress.

III. Contraindications in the use of ACTH, cortisone and hydrocortisone.

Primary Therapeutic Uses of ACTH, Cortisone and Hydrocortisone

Production of Remissions and Gaining of Additional Time for Preparation of Patients Undergoing Surgery: It has been well documented that ACTH and the adrenal steroids can produce a dramatic remission in patients with certain diseases that may require surgical therapy. These diseases can be divided into two broad categories: chronic inflammatory diseases of the intestines, such as ulcerative colitis[1-7] and regional enteritis[2, 8, 9]; and certain blood dyscrasias for which splenectomy may be indicated (hemolytic anemia, thrombocytopenic purpura, etc.).[11-21] The remarkable improvement which may occur when the aforementioned hormones are given in conjunction with the other well established forms of therapy to a patient with severe ulcerative colitis may eliminate or postpone the need for operation.[5, 6, 10] By the same token, if operation is necessary the improved preoperative status of the patient frequently allows the surgeon to complete the entire operation (ileostomy and total colectomy) in one stage rather than in multiple procedures. Previously, it was often necessary to perform an ileostomy in a critically ill patient as an emergency measure to improve his general state prior to the removal of the colon. The results in the treatment of patients with severe regional enteritis have not been so encouraging as those obtained in ulcerative colitis, although temporary remissions often occur.[2, 5, 8, 9]

The effectiveness of ACTH and the adrenal hormones in from 40 to 70% of patients with hemolytic anemia,[11-13] purpura with or without hypersplenism,[11, 12, 14-21] certain allergic states[4, 22-24] and rheumatic carditis[25-27] is now well known. It has been demonstrated that in such patients remissions might be obtained by giving ACTH or adrenal steroids, and operation may be temporarily or permanently avoided.[19, 21] When operation is required and the patient's condition is good, the use of these hormones is best avoided. In some patients with idiopathic thrombocytopenic purpura

and acquired hemolytic anemia who have a persistence of the disease or recurrence after splenectomy, remissions may be produced by ACTH or cortisone.[19, 21] Both the internists and the surgeons are cognizant of the dangers associated with the use of such therapy (uncontrolled or marked infection, gastrointestinal tract perforations, etc.), and should coöperate in the care of such patients.

Treatment of Surgical Disorders and Complications: The adrenal steroids have been used to treat thyroid crisis,[28, 29] pancreatitis,[30, 31] thrombophlebitis [31-34] and other surgical complications.[35-42] Since these preparations were used as adjuncts to the usual methods of therapy it is difficult to assess their real value. Because of favorable reports [28-34] of the use of these agents for the aforementioned conditions, it would seem logical to employ them after the usual methods of therapy fail to produce a desired response. While no exact measurements have been made to establish the effectiveness of such therapy, adrenal steroids may reduce the inflammation and in this way be of benefit. The exact rôle of these hormones in such conditions must await further studies.

Lewis and associates [43] reported that of 20 patients with severe tetanus, three alone survived when only the accepted measures were employed, while eight survived out of 15 alternated, comparable patients when they were given the same treatment plus oral cortisone or hydrocortisone. None out of five patients survived when cortisone was given intramuscularly. They conclude that the results obtained following cortisone or hydrocortisone administered orally are statistically significant and are consistent with the clinical observations, as well as with the previously reported beneficial effects they obtained by giving corticotropin. ACTH, cortisone and hydrocortisone have been used beneficially to treat subacute thyroiditis,[44] acute bursitis [35] and tenosynovitis.[4, 36] Experimentally, by either systemic [37-40] or local application,[41, 42] these hormones have been of some value in reducing the formation of intraperitoneal adhesions.

Endogenous or Iatrogenic Adrenal Insufficiency: The management of patients who are getting, or who have received within several months, therapeutic doses of ACTH or adrenal steroids, as well as persons with panhypopituitarism or Addison's disease who develop severe infections, are injured, or must undergo an operation, is now fairly well understood. The need for supplemental endocrine therapy during "stress" has been well emphasized by Salassa, Bennett, Keating and Sprague.[45] These workers have reported the dire results that may occur if inadequate treatment is given. During a period of "stress" such patients need an increased amount of adrenal corticoids. In a severe stress the administration of 200 or more mg. of hydrocortisone per day is often needed. As the stress subsides the dose is gradually reduced until, with recovery, the medication can be discontinued or, if necessary, a maintenance intake of 50 mg. or less per day is employed.

Aside from those individuals who develop hemorrhage [46, 47] or cytotoxic changes [48] in both adrenal glands (Waterhouse-Friderichsen syndrome), which usually is associated with an overwhelming infection, patients may occasionally develop adrenal insufficiency because of invasion or almost total replacement of the adrenal glands by tumor.[49] While acute adrenal insufficiency due to these causes is rare, the possibility of its occurrence must be always kept in mind so that proper therapy can be given. The most frequent causes for shock occurring during or after operation are hypovolemia resulting from external or internal bleeding, dehydration, electrolyte deficiencies, myocardial infarction or pulmonary embolus. If these causes have been ruled out or adequately treated and the patient remains in shock, the presence of an elevated eosinophil count is sufficient indication for treatment with adrenal steroids. If the patient's condition permits, it would be desirable to see if the eosinophils decreased after an infusion of ACTH. In many instances this delay might not be advisable, and hydrocortisone is best given intravenously immediately before the patient's condition further deteriorates. Again, the initial 24 hour dose of several hundred milligrams of hydrocortisone is gradually reduced over a period of two to five days to a maintenance level. After recovery, it is important to evaluate the adrenal function of these patients.

The adrenal-insufficient or totally adrenalectomized patient who develops an upper respiratory infection or a more serious complication should increase his intake of cortisone or hydrocortisone. It should be emphasized to the patient that it is extremely important that the medication be taken regularly and, if sickness or injury occurs, his physician should be called immediately. A patient who takes a daily maintenance dose of adrenal hormone should always carry a card stating his diagnosis and medication. It should also contain his physician's name so that, in the event of injury or unconsciousness, prompt and adequate therapy will be provided.

Endocrine Therapy in Shock and Peritonitis

Periodically during the last 20 years, adrenal cortical extract [50–57] and, more recently, ACTH, cortisone or hydrocortisone,[49, 58, 59] have been advocated in the treatment of shock or hypotensive states. Many of the workers who propose such therapy believe that its effectiveness is due to a restoration toward normal of the altered capillary permeability.

In 1930 Blalock [60] and Parsons and Phemister [61] demonstrated that in *traumatic shock* a shift of fluid and electrolytes occurred from the extracellular compartment into the traumatized area. Such a transfer of body fluid resulted in a reduction of blood pressure which could be accounted for by the decrease in circulating blood volume. The "local fluid loss" theory [60] has now been fairly well accepted as the primary cause of traumatic shock. It is important to differentiate this form of hypotension from dehydration and hemorrhagic shock, since in the latter conditions, unless anoxia super-

venes and is fairly severe, a significant increase in capillary permeability does not occur. In hypovolemic states (hemorrhage and dehydration), where capillary permeability is not increased, amounts equal to or in slight excess of a fluid comparable to that lost will result in a restoration of the circulating blood volume to near normal. However, where capillary permeability is increased (burns, intestinal distention, etc.), much of the fluid, electrolytes and colloids continue to leak out of the vascular system; thus replacement therapy has only a temporary effect.[62] Under the latter circumstances, continuous treatment must be given until the loss of fluid from the vascular compartment stops. It is apparent that the type, amount and duration of therapy needed in the various forms of hypotension will vary with the presence or absence of capillary permeability, loss of red blood cells, degree of sludging of blood, and the responsiveness and state of the peripheral vascular bed.

The work of Blalock, Beard and Johnson [63] demonstrated that the composition of fluid lost into the traumatized area was almost identical to that of plasma. Our studies have shown that the electrolyte composition of fluid removed from a blister following a thermal burn,[64] or from the translocated fluid found in the pleural or peritoneal cavities or small intestine,[65] is similar in composition to extracellular fluid. When capillary permeability is increased the total protein concentration of the fluid which is lost from the vascular compartment may reach 3.0 to 4.5 gm. per 100 ml., with the albumin fraction accounting for 75 to 90%. Randall [66] has well termed such accumulations of fluid the "third body fluid space." Our recent studies [67] have demonstrated that patients with intestinal obstruction may accumulate as much as 10 or 12 L. of fluid in the peritoneal cavity and gastrointestinal tract within eight to 16 hours. It is little wonder that patients with a volvulus or strangulated intestinal obstruction, severe trauma, perforated ulcer and similar conditions often become oliguric and hypotensive with little evidence of an external loss of fluid.

In 1933 Loeb, Atchley, Benedict and Leland [68] stated that "a characteristic clinical picture develops as the loss of inorganic base from the body progresses in diabetic acidosis, in severe diarrheas, in high intestinal obstructions and probably in certain other pathological states." They emphasized that clinically such patients exhibited "profound weakness, prostration, dehydration, anorexia, nausea, vomiting, fall in blood pressure, shock at times accompanied by anuria, retention of nonprotein nitrogen, and a decrease in the concentration of the chloride ion in the blood." These workers [68] showed that the urinary loss of sodium in the adrenalectomized animal and in patients with adrenal insufficiency was a very important factor, and that such patients or animals exhibited findings comparable to the other hypotensive states noted above.

Swingle and his associates [69-71] felt that, in the absence of the adrenal hormones, the blood water slowly transudes into the tissues and interstitial

spaces and is immobilized. While they believed that water and salt were, or might be, wasted to some extent through the kidneys, they felt that their work showed that this loss alone was not of a sufficient magnitude to cause the degree of extracellular dehydration and decrease in circulating blood volume which occurred. In spite of the fact that Swingle and his associates [70] stated that "the cortical hormone is probably not concerned with capillary permeability," many workers subsequently referred to their studies as demonstrating the effectiveness of adrenal cortical extract in combating increased capillary permeability. Swingle and associates [69-71] and Harrop [72] showed that in an untreated adrenalectomized animal the deteriorating state, and frequently the abnormal blood or serum values (hemoconcentration, hyponatremia and hypochloremia) could be corrected by giving adrenal cortical extract as the only therapeutic agent. These studies [68-72] emphasized that adrenal cortical hormones are an essential factor in the regulation and control of the internal distribution of water and electrolytes.

In spite of the work of Swingle [69, 70] and Harrop,[72] which indicated an internal shift of water and sodium, and the experimental evidence which demonstrated an increase in the cell water in adrenalectomized animals in a state of insufficiency,[73-75] many observers held to the belief that the major loss of water and sodium was due to the renal excretion of these substances, as advocated in 1933 by Loeb.[68] However, recent studies in totally adrenalectomized patients in a state of acute adrenal insufficiency support the earlier work of Swingle and Harrop. Pearson and his associates [76-78] reported that in totally adrenalectomized patients the urinary sodium was conspicuously absent during cortisone withdrawal. They also pointed out that a significant hyponatremia developed and that potassium retention was not observed, although signs of adrenal insufficiency were present. They noted in these patients that an antidiuresis resulted during cortisone withdrawal and a prompt water diuresis occurred on resumption of cortisone therapy. They also observed that rapid restoration toward a normal physiologic state occurred when the hormone was administered. In 1953 Hills, Chalmers and Webster [79] demonstrated, by means of water and electrolyte balance studies and changes in volumes of distribution of inulin and chloride, that large internal shifts of fluid and electrolytes occurred during periods of acute adrenal insufficiency in six adrenalectomized patients. In totally adrenalectomized patients we have noted that hyponatremia and symptoms of adrenal insufficiency may develop without a negative sodium balance, and on other occasions sodium wasting can occur.[80] It seems apparent, therefore, that hyponatremia and hypovolemia can develop in adrenal-insufficient states due to the external loss or internal shift of fluid or electrolytes, or because of a combination of both factors. Our studies [80] show that a fall in the serum sodium and rise in the potassium concentration can occur during periods of sodium retention and potassium wasting, and that the reverse (rise of the serum sodium and fall of serum potassium concentration) may

be seen during periods of sodium wasting and potassium retention. This reëmphasizes that serum and blood concentrations are poor guides to the state of excess or deficiency that might exist,[81-83] and that it is wrong to assume that either hyponatremia or hypokalemia is synonymous with a total body sodium or potassium deficit. Likewise, high blood or serum concentrations (hematocrit, protein, chloride, potassium and sodium) are not infrequently encountered when deficits of these substances exist.[81-83] It is apparent that overhydrated patients often show a low serum sodium concentration when a greater amount of water than sodium has been retained. Although an external sodium deficit has not occurred, our studies [80] in untreated adrenalectomized patients have shown that the symptoms and hyponatremia, hyperkalemia and hemoconcentration can be alleviated by the administration of either a hypertonic salt solution or hydrocortisone.

Many workers have reported that in burns [50-52] and surgical shock,[49, 54-59] and in patients with severe or fulminating infections,[84-90] adrenal cortical extract, ACTH, cortisone or hydrocortisone have been of great value. It should be noted that most of this work is based on clinical impressions, and since in almost every instance the conventional therapy was also given it is difficult to evaluate these reports.

Ramey and associates [91] and Fritz and Levine [92] in 1951 showed that the rise in blood pressure following an infusion of norepinephrine was less in an adrenalectomized dog than in a normal one. They also noted that a significant rise in blood pressure occurred in adrenalectomized animals receiving adrenal cortical extract and simultaneously an intravenous infusion of norepinephrine. It has also been demonstrated by Zweifach, Shorr and Black [93] that in adrenal-insufficient animals norepinephrine failed to cause its usual response of the terminal vascular bed, and that by the addition of cortisone a normal vascular tone could be restored. These workers believed that in the late stages of adrenal insufficiency in their experimental animals (adrenalectomized rats) capillary permeability was increased. These contributions are of great interest and demonstrate that the adrenal steroids seemingly complement the effect of norepinephrine. However, since the restoration and maintenance of the plasma and interstitial fluid volumes to normal are the therapeutic objective in traumatic shock (tissue damage due to burns, injury, etc.), the use of vasopressors is felt to be contraindicated under such circumstances. *It should be remembered that a deficit of vasopressor substances or adrenal corticoids has not been shown to occur in traumatic shock. In fact, studies which pertain to the problem show that greater than normal amounts of cortin* [94-97] *or corticosteroids* [98-103] *and adrenalin* [104-106] *are present.* Menkin [107, 108] and Benditt and his associates [109] found that adrenal cortical hormones (ACE and cortisone) negate the effect of leukotaxin, cell free exudates and hyaluronidase to increase vascular "permeability." These workers measured the vascular permeability by determining the extent of transudation of fluid in animals.

Many experimental and clinical studies [50-59, 113-120] have been reported where adrenal cortical extract, ACTH, cortisone or hydrocortisone has been employed in an attempt to alleviate shock. These hormones apparently have a beneficial effect in combating anaphylactic shock, especially if they are given early.[110-112] In experimentally induced traumatic or hemorrhagic shock they have apparently minimized the effects and reduced the mortality rate when the animals were *pretreated* with adrenal cortical extract or desoxycorticosterone acetate, but have had no apparent beneficial effect when given after "shock" has been induced.[113, 114]

As early as 1936, adrenal cortical extract was employed in the treatment of shock resulting from a thermal burn,[50] and subsequent clinical reports have stated that adrenal cortical extract [51, 52] and, more recently, ACTH [115-117] have been of value in reducing the fluid and electrolyte loss into the wound. However, no demonstrable beneficial effect has been noted in the experimental burned animal following the use of ACTH, cortisone or desoxycorticosterone acetate.[118-120]

In 1944 Swingle and Remington [121] reviewed the role of the adrenal cortex in physiologic processes, and in their discussion of the use of ACE and DOCA to combat hypotension stated: "It is apparent that in very few instances has the degree of protection reported against shock been of sufficient magnitude to warrant the conclusions that the stress procedure has induced circulatory failure by reason of a sudden partial adrenal insufficiency." They also stated: "Since there is no evidence of a primary failure of tissue metabolism in shocked intact dogs, it is not surprising to find that cortical hormones are without marked effect in increasing the normal resistance to shock." Although more work has appeared recently employing newer methods and specific steroidal hormones in the treatment of shock, no evidence seems to have been presented which would alter Swingle and Remington's conclusions.

Galante, Rukes, Forsham and Bell [58] and their associates [59] published studies on a 30 year old woman who, two days postoperatively, was apparently deteriorating rapidly and was unresponsive to vasoconstrictor drugs. One hundred milligrams of hydrocortisone in 1,000 c.c. of 5% dextrose in water were administered intravenously over a two hour period, and several hours later her blood pressure rose from 90/70 to 124/90 mm. of Hg, and her skin became dry and warm. They believed "this immediate dramatic beneficial and life-saving effect" was brought about by the administration of hydrocortisone. Although this might well have been the case, there was no objective evidence to show that adrenal insufficiency existed, or that the patient might not have made a similar recovery had only the 5% dextrose in water been given. It is particularly difficult to evaluate the effectiveness of this therapy in such a patient who, because of mitral insufficiency with auricular fibrillation, had been kept on a restricted sodium intake (350 mg. per day) and had been given mercurial diuretics and

digitalis preoperatively. With the insensible fluid loss and water and electrolyte shifts that might occur during and after the operation, and the profuse continuous diaphoresis that she exhibited postoperatively, it is quite possible that such a case would do better when given water rather than norepinephrine. We have reported [122] equally dramatic recoveries in two seriously ill women who developed hypotension and oliguria because of the translocation of fluid and electrolytes following hypodermoclysis of a non-sodium-containing solution. These cold and clammy hypotensive patients received normal saline intravenously, and several hours later made equally dramatic recoveries. If hydrocortisone had been included in the intravenous infusion, and fluid shifts and electrolyte needs in these patients had not been recognized, it would have seemed logical to conclude that this hormone had achieved an almost miraculous result.

It is quite apparent that occasionally patients with suppressed or no adrenal cortical function may be encountered and would obviously require hormone therapy. It is also evident that occasionally patients who fail to have a fall of their circulating eosinophils,[123] or rise in the blood or urinary 17-hydroxycorticoids, may withstand the trauma of a thermal burn [99] or major surgery [124] without receiving exogenous hormone therapy. With the rare exception of patients who have partial or complete destruction of the adrenal glands, there is no evidence that adrenal exhaustion occurs. In traumatic shock, the routine use of adrenal cortical hormones should await the demonstration that such therapy causes a restoration of circulating blood volume, or that by its early administration the increase in capillary permeability can be reduced or prevented and the transudation of fluid and electrolytes diminished. Reliance on the adrenal steroids could well lead to a failure to establish and treat the true cause of the patient's hypotensive state. In most instances this will be the result of blood, water and/or electrolyte deficiencies. Although it is apparent that the clinical appearance and many of the blood findings (reduced plasma volume, hyponatremia, etc.) are comparable in patients with hypovolemia and hypotension due to adrenal insufficiency and other shock states, there are certain underlying differences in the two conditions.

The most important factor in these two conditions is the state of adrenal activity, which can usually be differentiated by an eosinophil count. The history of the patient is obviously very important, and one might also find considerably more sodium in the urine of the adrenal-insufficient patient than in that of the individual in shock from other causes, although this would depend upon the preëxisting sodium intake and the cause of hypotension.

In spite of the favorable reports [89, 90] following the use of adrenal hormones in recognized severe infections, objective evidence of their influence in these conditions is needed before they can be advocated. In a recent paper concerning the use of ACTH and the adrenal steroids in the treatment of severe infections, 40 of the patients discussed had peritonitis.[89] The

authors summarize the results in this group of patients as follows: There were 16 cases with beneficial effects, 12 probable, two uncertain and 11 cases with improbable effects. Seventeen of the 40 patients died, giving a mortality rate of 42.5%. It has been stated [90] that "by temporarily inhibiting the systemic toxicity [resulting from severe infections] one may buy time and enable the individual to survive until the antibiotics have an opportunity to take effect." It has also been emphasized that a precise regimen must be followed, and that antibiotic and supportive therapy should not be neglected or disaster may result.[90] Hume stated that even when antibiotics were employed it was dangerous to use ACTH or adrenal corticoids in patients with severe infections.[31] From the evidence available at present it would seem desirable to give adrenal corticoids to only the occasional patient with peritonitis who had adrenal insufficiency due to panhypopituitarism, prior hormone therapy, Addison's disease, Waterhouse-Friderichsen syndrome or a prior adrenalectomy. Obviously, controlled experimental studies are necessary to settle this important problem before further clinical trials can be advocated.

Partial or Total Adrenalectomy

The availability of cortisone and, subsequently, hydrocortisone has made subtotal or total adrenalectomy a relatively safe procedure. Subtotal or bilateral total adrenalectomy has been performed in patients with hypertension,[125-128] Cushing's syndrome,[129-133] primary aldosteronism,[134] adrenogenital syndrome [135-137] and pheochromocytoma.[138, 139] Total adrenalectomy has been employed in a cirrhotic with ascites,[140] and for palliative treatment of metastatic carcinoma of the breast and prostate.[141-149] Following subtotal adrenalectomy, even though some active adrenal tissue is left, such patients frequently may need 200 mg. of hydrocortisone or more on the day of surgery, with gradually diminishing doses. Several weeks after operation it is necessary to determine whether any maintenance therapy is needed. This is best determined by noting the response of eosinophils or 17-hydroxycorticoids to ACTH after 12 to 48 hours of withdrawal of all adrenal steroid therapy. Periodic reëvaluation of such patients is required, since the remaining adrenal tissue may atrophy or hypertrophy and thus the requirements of the patient would vary.

For Diseases of the Adrenal Gland: S. M., a 38 year old housewife with severe, long-standing changes typical of Cushing's syndrome demonstrated remarkable improvement following bilateral adrenalectomy.[130] A comparison of the findings (table 1) prior to operation with those following total adrenalectomy shows that her weight returned to near normal, the blood pressure has fallen to and remained at normal levels, the circulating eosinophils have risen, fasting blood sugar has returned to normal, plasma proteins have increased, and the plasma cholesterol and alkaline phosphatase, as well as the urinary 17-ketosteroids, have returned to normal. From

a severely depressed, paranoid person who required institutional care, the patient has become a cheerful woman of normal appearance and actions. The diabetes, hypertension, psychosis, marked obesity and associated moon-face, buffalo hump, hirsutism, purplish abdominal striae, amenorrhea, acne and muscular weakness have all disappeared. The intravenous glucose tolerance curves done on this patient preoperatively, during the period of hypercorticism and several months postoperatively are shown on the right-hand side of figure 1. In contrast, an intravenous glucose tolerance curve (1 gm. of glucose per kilogram per hour) is shown on the left-hand side of figure 1 in a patient before and after a major upper abdominal operation. It will be noted that this patient showed a normal curve preoperatively and a diabetic-like curve two days postoperatively. Such changes are seen frequently following operative "stress," and are believed to result from an increased activity of the pituitary-adrenal axis.[150, 151] The results were so

TABLE 1

Effect of Total Adrenalectomy on Body Weight, Blood Pressure and Blood Constituents in a Patient with Cushing's Syndrome

Determination	Before Operation	After Operation		
		7 wk.	6 mo.	13 mo.
Weight, kg.	77.5	69.2	60.0	55.0
Blood pressure, mm. Hg	180/120	140/105	130/80	105/70
Circulating eosinophils/cu. mm.	0.0	—	412.0	860
Fasting blood sugar, mg./100 ml.	261.0	100.0	69.0	80.0
Plasma proteins, gm./100 ml.	5.1	7.3	—	7.0
Plasma cholesterol, mg./100 ml.	634.0	257.0	367.0	248.0
Alkaline phosphatase, units*	9.0	10.7	—	3.5
17-ketosteroids, mg./24 hr.	25.8	6.9	5.4	9.0

* Shinowara units; each equals approximately 1.8 Bodansky units.

gratifying in this patient (S. M.), whose hyperplastic adrenal glands weighed slightly over three times the expected normal, that we feel a total adrenalectomy is the operation of choice for this disease, unless it is of short duration or a unilateral tumor is found.

The benefits derived from total adrenalectomy for metastatic cancer are still equivocal. Most of the patients that have been operated upon for metastatic melanosarcoma have derived no benefit.[144, 147] Although some workers report [141, 142, 144] beneficial results in patients with metastases to bone from carcinoma of the prostate, it is generally felt that the results are not so good in such patients as those noted in cases with metastases from cancer of the breast. In most patients with osseous metastasis from carcinoma of the breast, symptomatic benefit has been obtained, but objective improvement is encountered less frequently. Generally, the patients with soft tissue metastasis do not show as good a response as do patients with skeletal lesions. Rarely do metastases to soft tissue or bone regress sig-

nificantly or disappear. However, many patients with disabling pain, spontaneous fractures and nerve pressure from metastatic lesions show sufficient improvement for from six to 30 months to make the procedure worth while in those to whom little else can be offered.

The management of patients undergoing total adrenalectomy has been relatively simple. It is our feeling, as advocated by Albright,[152] that all patients with adrenal cortical hyperfunction should have testosterone propionate, 50 mg. intramuscularly three times weekly, or one of the longer-acting derivatives, prior to operation to aid in correcting the catabolic effect of the adrenal hyperactivity. A continuous intravenous drip of 10% dex-

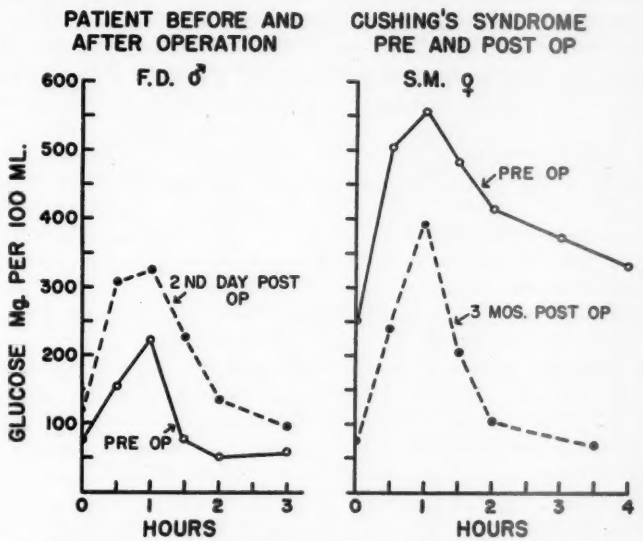

FIG. 1. F. D. Intravenous glucose tolerance curves before and two days after an upper abdominal operation (left). Glucose tolerance curves in patient (S. M.) with Cushing's syndrome before and after total adrenalectomy (right).

trose containing 200 mg. of hydrocortisone is begun before surgery or at the time the adrenals are removed. This infusion is regulated so that it is given continuously over 24 hours. The dose of hydrocortisone is reduced daily by 25 to 50 mg. until a maintenance intake of 40 to 50 mg. is reached. The patient can be shifted to oral medication and diet when intestinal peristaltic activity returns. To avoid periods of overtreatment and undertreatment during the 24 hours, the daily needs of hydrocortisone should be given in four or more divided doses. We have given blood preoperatively to correct any preëxisting deficit or anemia, and at the time of operation an amount equal to or in slight excess of that lost. It has also been

our practice to provide an adequate dextrose and amino acid intake through a second needle or cannula so that hypoglycemic shock can be avoided and the nutritional needs at least partially met during the period before an adequate oral intake is resumed. The total fluid and blood intake is limited to from 2,500 to 3,500 ml., unless additional blood is needed, and to from 75 to 150 mEq. of both sodium and potassium daily. In the first 24 to 48 hours postoperatively it has been found helpful to follow the patient's hourly urinary output, since a drop below 50 ml. per hour may indicate an impending hypotension. If hypotension occurs after the aforementioned program has been instituted, norepinephrine is given. If a restoration of the blood pressure occurs, small amounts of this material can be administered to maintain a normal pressure. In some patients norepinephrine may not be necessary, while in others small amounts are needed, but it is rarely necessary after from six to 24 hours postoperatively. In the event that the described regimen does not maintain a normotensive state, it is apparent that a complication (hemorrhage, pneumothorax, etc.) has occurred and must be diagnosed and treated.

Friedell and Storaasli [153] have employed radioactive phosphorus (P^{32}) in patients with osseous metastases from carcinoma of the breast. They demonstrated in normal rats that most of the radioactive phosphorus was taken up in the bone. They also had some patients who showed x-ray evidence of regression or recalcification of osseous metastases following the administration of P^{32}. In studies still in progress, done in conjunction with these workers, we have measured the radioactive phosphorus uptake in such patients before and after adrenalectomy.[80] The amount of P^{32} retained by the body is greater after adrenalectomy than before. Radioautograph of removed sections of ribs containing a metastatic lesion shows that most of the detectable P^{32} is located around the metastatic tumor. While we have treated only four patients with P^{32} after total bilateral adrenalectomy, these cases have apparently shown fewer side effects from the phosphorus and have seemingly received more benefit than would have been derived from either treatment alone. Obviously many more observations are needed before the exact effect of such combined therapy is known. However, since adrenalectomy alone offers a relatively short period of relief to such patients, it would seem that the future of this operation depends upon the ability to select only those patients who will show maximal benefit, or, by combining it with radioactive phosphorus or some other therapy, to prolong the benefit and duration of inhibition of neoplastic growth. At present it is our feeling that total adrenalectomy for metastatic breast carcinoma, which is still in the investigative state, should be done only in those institutions that can follow the patients carefully and evaluate the results in order that the true value of this procedure can be ascertained.

The results following subtotal adrenalectomy for pheochromocytoma are usually excellent.[138, 139] In most instances a partial or total removal of the

adrenal gland containing the tumor is sufficient, but occasionally bilateral involvement may necessitate complete adrenalectomy. In these latter patients the maintenance therapy is essentially the same as previously mentioned except that large amounts of norepinephrine may be necessary for several days.

Wilhelm and Marks [136] have reported the use of cortisone and/or subtotal adrenalectomy for the treatment of sterility in women with adrenogenital syndrome. The results obtained, and those reported by other workers,[135, 137] indicate that sterility in women caused by androgenic adrenal cortical hyperfunction may at times be reversible. Such a patient with a neoplasm requires surgical therapy, whereas those patients who have hyperplasia of the adrenal glands may be properly treated with cortisone. In an attempt to differentiate a tumor from hyperplasia of the adrenal gland, Jailer and Wallace [154] reported giving 100 mg. of hydrocortisone in 500 ml. of dextrose and water intravenously over a four hour period and collecting urine for four hour periods before, during and for 16 to 24 hours after the infusion. The urinary 17-ketosteroids will decrease in patients with adrenal hyperplasia and will be unaffected in patients with neoplasia. Small amounts (1 to 2 mg. daily) of 9-alpha fluorohydrocortisone may also inhibit ACTH secretion and thus lead to a reduction of the adrenal cortical activity. However, if a tumor is present its secretion is unaffected, since it is not governed by pituitary activity. If the signs and symptoms cannot be controlled by adequate hormone therapy in patients with the adrenogenital syndrome due to hyperplasia, adrenalectomy should be considered.

The results [125–128] of total or subtotal adrenalectomy for essential hypertension, with or without sympathectomy, are still equivocal. Since this is a rather drastic and inconsistent way of reducing the blood pressure, and in many patients apparently accomplishes only what sodium restriction and other conservative methods will do, it seems doubtful that this procedure will be employed to any great extent in the future.

The removal of part or all of the adrenals for primary aldosteronism is intriguing and certainly, from the report of Conn,[134, 155] appears to hold great promise. It is apparent from the reports of Conn,[134, 155] Evans and Milne [156] and Mader and Iseri [157] that in this condition sodium retention and potassium wasting occur, and that there is some interference with the renal tubular reabsorption of water. Thus, a hypokalemia, hypernatremia and alkalosis result, with intermittent muscular weakness, paralyses, polyuria, polydipsia and hypertension.

Patients with cirrhosis of the liver with ascites have been demonstrated [158–161] to have a very low excretion of sodium in the saliva, sweat, urine and feces.[162] It has also been demonstrated that the urine from such patients contains larger than normal amounts of a sodium-retaining substance which is presumably aldosterone.[163, 164] It is believed that such patients do not secrete an increased amount of adrenal steroids but fail to

conjugate or remove these substances at a normal rate because of impaired liver function (secondary aldosteronism). Experimental evidence [165, 166] and clinical studies [167] support this view. In animals, experimentally induced ascites and positive sodium balance have been eliminated following bilateral adrenalectomy.[168] These animals have been kept in good health without ascites following adrenalectomy by the daily administration of cortisone. Marson [140] reported considerable improvement following a bilateral adrenalectomy in a cirrhotic patient with ascites. It might appear that this is a drastic way of eliminating ascites, but it should be remembered that few patients with severe cirrhosis, who require frequent paracenteses, will survive for much more than six months.[169] It has been demonstrated [160, 170] that cirrhotic patients with ascites in the late stages of their disease may show improvement if hospitalized for from six to 12 months, with ideal dietary management. However, since such therapy is rarely feasible, adrenalectomy might be considered in selected patients.

Factors Governing the Metabolic Response of the Patient to "Stress"

Although Cuthbertson [174, 175] had earlier described the "post-shock metabolic response" in patients with fractures, and Howard [176] had made similar studies, only sporadic reports and incomplete balance studies had been done on patients with other injuries or following operation. J. S. L. Browne [94, 177] and Dorfman [95] and their associates had shown, by bio-assays, that substances were present in the urine of normal or postoperative patients which extended the life of adrenalectomized rats subjected to cold. This extract from human urine was called cortin, and subsequent studies by our group [96] and by Shipley and his associates [97] proved it to be present in the urine of burned patients in amounts well above the trace quantities that could be identified in the urine from normal people. The results of the metabolic balance studies of these same patients showed sodium, chloride and water retention and nitrogen and potassium wasting for the first two days. A potassium and nitrogen deficit and sodium, chloride and water retention usually occurred during the first day or two following a thermal burn. Subsequently, with the exception of the nitrogen balance, the reverse was usually encountered, although the urinary cortin levels were as high during the first two days, or considerably higher. It was thus apparent that after several days the burned patient was unloading sodium, water and chloride while retaining potassium, although adrenal overactivity still persisted. Furthermore, studies done at that time,[64, 96, 171–173] and subsequent observations on postoperative patients [65, 67, 151, 178] have shown that the electrolyte balance and nitrogen wasting can be modified by providing a different intake of certain nutrients or by using testosterone propionate.

Recent work by Conn [179] and by Moore [99] and their associates shows that the level of 17-hydroxycorticoids in the urine does not necessarily

parallel the type or magnitude of the metabolic response to "stress." By employing ACTH, typhoid antigen and pyromen, Conn, Fajans, Louis, Seltzer and Kaine [179] demonstrated in four men of comparable ages that different stressor agents produced different metabolic responses. Moore and his co-workers [99] reported that a normal individual showed an almost identical metabolic response over two four-day starvation periods, although during the second period fairly large amounts of cortisone were given for two days. The amount of weight lost and the negative sodium, chloride, potassium and nitrogen balances were of essentially the same magnitude on both occasions. The blood eosinophil count and 17-hydroxycorticoids in the urine showed no evidence of adrenal overactivity during the first four-day starvation period, but a definite rise of the 17-hydroxycorticoids and marked fall of the circulating eosinophils occurred during the second four-day starvation period when cortisone was given. These authors [99]

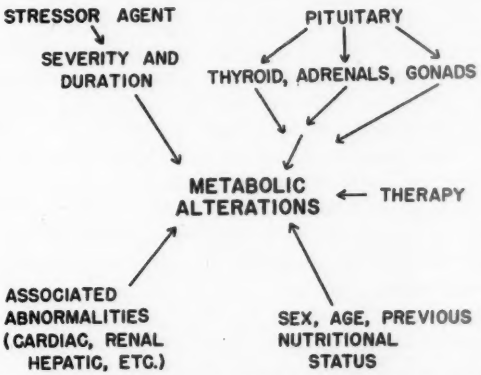

FIG. 2. Factors influencing the metabolic response to "stress."

conclude in this study that there was a close relationship between the amount of 17-hydroxycorticoids in the urine and the nitrogen deficit during the first few days in patients following operative trauma. A perusal of their data shows that a patient with a thermal burn showed a negative nitrogen balance for 21 days, during which time the 17-hydroxycorticoids were normal. On the other hand, a woman undergoing a radical mastectomy showed a persistently elevated 17-hydroxycorticoid output for over two weeks and only a moderate nitrogen deficit for a few days, which was no larger than the normal nontraumatized subject showed on a daily 400 calorie intake. From the inconsistent relationship between the metabolic balance studies and 17-hydroxycorticoids in these three patients, such conclusions do not seem justified.

A variable pattern of metabolic alterations has been shown to occur in

comparable patients following a "stress" of similar magnitude and duration (the administration of varying amounts of cortisone,[180] or operations [65, 67, 151, 178] or burns.[171, 172]) It is apparent that the stressing agent, endocrine response, age, sex, previous nutritional status, the concurrent disease (brain, liver, kidneys, heart, endocrine, etc.) and the therapy employed are factors which govern the type and magnitude of the metabolic alterations (figure 2). Many workers (Ingle,[181] Engel,[182] Conn,[179] Sayers [183]) agree that under conditions of "stress" the adrenal cortical hormones exert a "normalizing" influence, and that one is not justified in believing that a stereotyped metabolic response takes place after comparable injuries, or after any circumstances sufficient to excite pituitary-adrenal hyperfunction.

Contraindications and Dangers

ACTH and adrenocortical hormones should be administered rarely, if ever, in patients with Cushing's syndrome, peptic ulceration, psychoses, uremia, congestive heart failure, coronary artery disease, diabetes or malignant hypertension.[34, 58, 184] These agents are to be used cautiously in patients with tuberculosis, since it may well cause an exacerbation or spread of the disease. Most of the experimental work[185-187] and early clinical trials [188, 189] indicated that the use of cortisone or hydrocortisone enhances the spread or development of tuberculosis. However, some recent clinical observations [190-192] show that when it is used in conjunction with streptomycin and para-aminosalicylic acid beneficial results can be obtained. Rome and Braceland [193, 194] felt that the major psychic alterations noted during cortisone and ACTH therapy usually represented an intensification of a preexisting personality disorder.

Variable reports on the effect of wound healing of the skin [195-202] and underlying tissue (fascia, bone, etc.) [203-205] and of intestinal anastomosis [206] have been published. From the information available and the known metabolic effect of these hormones on carbohydrate, protein, electrolyte and water, it would appear that little difficulty would be encountered when ACTH and the adrenal steroids were given in modest doses for several weeks or less.[202, 207, 208] When large doses are needed for fairly prolonged periods of time, especially in malnourished patients, wound dehiscence or interference with wound healing might occur.[200] Occasionally ACTH and the corticoids have been advocated for use preoperatively and postoperatively in old or debilitated patients for their antipyretic, euphoristic and neuromusculotonic effect.[4, 58] While these agents might occasionally be of value in this regard, it would seem desirable to employ testosterone propionate or one of its longer acting derivatives in preference to or, if need be, in conjunction with ACTH or the adrenal steroids.[152, 209, 210]

A number of reports [211-222] also exist of complications that have occurred during treatment of rheumatoid arthritis and other conditions which resulted from, and in some instances were masked by, ACTH or adrenal

corticoid therapy. The occurrence of osteoporosis and fractures has been reported,[221, 222] and represents other serious sequelae which might occur after the prolonged administration of these hormones. It is apparent that the physician must decide whether the benefits to be gained by using these hormones will offset the risks and undesirable side-effects of such treatment. A thorough history and examination should be made prior to starting treatment, and the patient should be checked again if complaints or sickness occurs.

Conclusions

In this paper we have attempted to summarize both the therapeutic benefits and the dangers associated with the use of ACTH, cortisone and hydrocortisone in surgical patients. It is obvious that, in those patients who have acute or chronic adrenal insufficiency as a result of disease or surgical extirpation of the adrenal glands, the use of cortisone or hydrocortisone is mandatory. In other patients these hormones may be of value in avoiding operation, improving the preoperative status of certain desperately ill patients, or relieving some of the postoperative complications.

While these hormones represent a significant contribution to our armamentarium, it should be remembered that when given to surgical patients they can produce a wide variety of responses, many undesirable. It is also apparent that more studies are needed before these compounds can be widely used for some of the conditions for which they have been advocated. The interesting and enthusiastic reports concerning the clinical use of ACTH and adrenal steroids which have appeared should act as a stimulus for further study.

Summario in Interlingua

Le objectivo del presente reporto es summarisar le usos e periculos de ACTH, cortisona, e hydrocortisona in patientes chirurgic. In patientes con acute o chronic insufficientia del glandulas adrenal in consequentia de morbo o excision chirurgic, le uso de cortisona o hydrocortisona es imperative. Iste gruppo include patientes subjicite a adrenalectomia total in le curso del tractamento de syndrome de Cushing o in le effortio a palliar carcinoma metastatic del osso originari in pectore o prostata. Suppression pituitari e adrenal con resultante insufficientia adrenal es etiam a observar in individuos tractate prolongatemente con le steroides adrenal pro altere morbos, como per exemplo arthritis rheumatoide, etc. Tal individuos require supplementos de cortisona o hydrocortisona quando illes es subjicite a periodos de stress, debite per exemplo a operationes chirurgic, infectiones, o trauma. Durante tal periodos de stress, le individuo debe reciper usque a cinque vices su diurne dose de mantenentia del hormon.

Iste hormones pote etiam devenir de valor per producer dramatic remissiones in patientes con colitis ulcerative, anemia hemolytic, thrombocytopenia, etc. quando le necessitate de effectuar un intervention chirurgic pro un de iste disordines es a considerar. In le passato il occurreva frequentemente in tal casos que le intervention chirurgic esseva recommendate solmente post que le condition del patiente habeva devenite critic. Isto resultava in le necessitate de hastive preparationes, e a vices operationes a duo o tres phases esseva requirite. Le uso de ACTH, cortisona, o hydrocortisona in le tractamento de tal morbos suffice frequentemente pro alterar le

curso clinic de maniera que adequate preparationes deveni possibile e que un definitive operation pote esser effectuate con minus risco e melior resultatos.

Le function de ACTH, cortisona, e hydrocortisona in le tractamento de peritonitis, infection, e choc es non ancora clarmente establite. Ben que il ha essite asserite que iste substantias ha multe effectos benefic in choc e sever infectiones, le majoritate del clinicos ha administrate hydrocortisona conjunctemente con altere ben acceptate typos de therapia. Assi il es difficile determinar si le droga o le therapia de supporto esseva responsabile pro le effectos obtenite. Pro demonstrar efficacia in casos de choc il es necessari demonstrar que le hormones steroide restaura le volumine del sanguine circulante per transferer fluido a in le systema vascular o que illos reduce le transsudation de fluido e electrolytos a in le area del lesion per restaurar le normal permeabilitate capillar. In animales adrenalectomisate multes del supra-mentionate effectos occurre demonstratemente post le administration de hormones adrenocortical. Sed proque le majoritate del studios in patientes human indica que "stress" resulta in un sequela de hyperplasia del glandula adrenal con augmentate production del 17-hydroxycorticoides, on ha pauc ration a creder que le conditiones clinic e experimental es comparabile. Fider se al uso de cortisona o hydrocortisona in casos de choc traumatic pote ducer le medico a non establir e non tractar le ver causa del stato hypotensive de su patiente.

Le advenimento de cortisona e hydrocortisona ha rendite possibile adrenalectomia total e constitue un adjuta in le tractamento de patientes subjicite a adrenalectomia subtotal pro syndrome de Cushing, pheochromocytoma, o aldosteronismo primari. ACTH ha essite de grande valor in le evalutation periodic del activitate functional del remanente texito adrenal. Adrenalectomia bilatere ha essite effectuate pro palliar carcinoma metastatic, hypertension, o aldosteronismo secundari. Le mantenentia de iste patientes es relativemente facile con iste drogas, ben que le doses debe esser augmentate quandocunque le patiente suffre un infection, operation chirurgic, o trauma.

Iste hormones representa un significative addendo a nostre arsenal, sed on non debe oblidar que in patientes chirurgic illos pote producer un grande varietate de responsas, le quales es non semper desirabile. Il es etiam evidente que plus investigationes es requirite ante que on pote usar iste compositos routinarimente pro alicunes del conditiones pro le quales lor uso es nunc suggerite.

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PLASMA CREATININE CONCENTRATION AND CREATININE CLEARANCE IN CLINICAL WORK*†

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OUR reason for writing this paper is the wish to sum up salient points concerning the endogenous creatinine clearance with special regard to the utility of the test in routine clinical work. We intend to stress the differences in the requirements for a renal functional test suitable for research work and one fit for clinical routine. We will emphasize that this difference does not put any stamp of inferiority on the latter: it is here a question of utility.

We also wish to describe our laboratory procedure, which secures reliable results with relatively simple equipment. Many who have wanted to adopt this method have met with difficulties which may be conquered relatively easily.

At first some words about the term "renal functional tests." This term is not very accurate. The relation between functional tests like creatinine and other clearance tests and the renal function, the acid-base regulation, the electrolyte regulation, the water metabolism, etc., is more or less indirect. None of the clearance tests in use can tell more than a one-sided story about what is going on. The clearance tests tell us, at least under physiologic conditions, something about partial functions such as glomerular filtration, tubular reabsorption, renal blood flow, etc. But even here, time has shown that such exploration of partial functional patterns has proved of little help in clinical diagnosis and prognosis. The fact remains that in clinical medicine the utility of a test lies in its ability to tell us whether renal function is reduced, and to what degree, without regard to its dependency on glomerular or tubular function. This can easily be seen when considering the widespread use, especially in the United States of the phenolsulfonphthalein test, which depends largely upon tubular excretion, and, for instance, the endogenous creatinine clearance test, which depends upon glomerular filtration. In renal disease these two types of tests may be used with about the same advantage. To get something more out of a combination of such tests, a sort of normal contra an abnormal pattern has not met with success.

Generally speaking, a good renal functional test determines the excretion of a substance in the urine, and takes the following three factors into consideration: the rate of urinary flow, and the simultaneous concentration of the substance in question in plasma and urine. The clearance concept is

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† In this paper *creatinine* denotes the endogenous substances which yield color with alkaline picrate ("Jaffé-positive substances").

developed on the basis of a combination of these three factors. Historically, the definition came afterwards, but we do not need at the moment to concern ourselves with that, because the definition does not necessarily concern the test as a clinical renal functional test. The point is that, by dividing the urinary concentration of a substance with the plasma concentration and multiplying the ratio with the urinary flow (diuresis per minute), one gets a standardized procedure that may be used for any substance excreted in the urine. The formula does not tell anything about how the excretory process is accomplished. It is important to stress that the clinical utility of such a clearance test is independent of how the kidneys manage this "clearance."

It is thus of no importance whether creatinine is diverted into the urine solely by glomerular filtration or, under certain circumstances, by additional tubular excretion. Some writers have maintained that this deprives the endogenous creatinine clearance of its value. This is a great mistake, which may originate partly from confusing two things: one, the utility of a test as a measure of kidney damage; the other, the usefulness of the method as an exact measure of the true glomerular filtration rate. It is doubtful if one can measure the glomerular filtration rate with any test in the presence of an extensive renal lesion, but this is entirely beside our purpose, which is to find a method which is simple to carry out and which at the same time yields a reliable measure of the degree of renal damage. There are in fact at present only two tests of this kind which rival each other in clinical work, viz., the urea clearance test and the endogenous creatinine clearance test. Historically, the urea clearance test was developed far ahead of the creatinine clearance test, and is also today the most widely used. In the hands of trained pathologists and physicians the urea clearance test is admirable. But it is a fact, which we have emphasized in earlier publications,[1, 2] that the urea clearance test is unsuitable for physicians who are less well acquainted with renal physiology and pathophysiology. Sentimental reasons certainly play a great part in the adherence to the urea clearance test.

The main weakness of the urea clearance test is its dependency on the rate of urine flow. This necessitates the use of two different formulas, depending on whether diuresis is above or below 2 ml. per minute. Not one physician in a hundred understands and can explain why this is so, and what the square root sign in "the standard clearance" formula signifies.

The chemical method for urea determination is satisfactory, regardless of whether one uses the manometric method of Van Slyke or the Conway method. But these methods are cumbersome. It has been stressed many times that, apart from water, urea is the quantitatively most important substance of the urine, and the chief end product of the protein metabolism. This has been used as an argument for the use of urea clearance instead of creatinine clearance. But this is a theoretic consideration that we need

not take too seriously, the more so when we know that in the laboratory the small amounts of creatinine found in the plasma are determined with the same exactitude as the large amounts of urea.

But there are several peculiarities in creatinine metabolism that may prove to be of importance. Long known is the noteworthy constancy of the daily amounts of creatinine excretion in humans. This constancy is so great that it may serve as a reliable control of the urine collection in the wards. A change in the daily excretion of creatinine is almost invariably due to a faulty collection of urine. Less known is that, although there may be a considerable difference, relatively speaking, between the creatinine level in different individuals (as a rule one find values between 0.60 and 1.30 mg./100 ml. of plasma), the plasma creatinine value in the single individual is remarkably constant over a prolonged time. Deviation of more than 0.10 mg./100 ml. usually points to a faulty technic. It would certainly be of interest to study more closely the reasons for the difference between the plasma creatinine levels in different normal individuals. It is already known that the muscular mass plays a rôle, but there are several points here that still need elucidation.

The weakness of the creatinine method is that the chemical method, the alkaline picrate reaction, is not quite satisfactory. Much would be won if a better method were available. By the aid of Lloyd's reagent one certainly can estimate true creatinine with great exactitude, but this method is time consuming and unsuitable for clinical routine work.

Apart from the chemical determination, the endogenous creatinine clearance is a renal test that satisfies any claim. It is simple, and the creatinine excretion is independent of the volume of the diuresis. Plasma creatinine is to a great extent and to all practical purposes independent of the food consumption. Some authors state that they take care not to let the patient eat roasted meat, because roasting will convert creatine into creatinine. This is a precaution that is easy to take, although it is unnecessary unless the patients want to consume excessive amounts of roasted meat.

The statements made here are all known facts that need no documentation. But as in any clearance method, the creatinine clearance depends upon accurately collected and measured urine volume. It is curious to see how little this crucial point is appraised. The bladder must be emptied to the last milliliters both at the beginning and at the end of the test period. Unless this is done the test is of no value, and this goes for all clearance methods. The smaller the diuresis, the larger the error introduced by faulty bladder emptying. For that reason diuresis is enhanced by drinking water beforehand. We have for some years been using 24 hour creatinine clearances, for the reason that the error introduced by faulty urine collection will be less the larger the urinary volume. But this 24 hour test also has its weaknesses. The patient must be kept under close observation, and under the care of trained nurses. If several 24 hour periods are run, a

distinct disagreement usually points to faulty urine collection, as mentioned above.

Because of this weakness, common to all clearance methods, the creatinine determination has one advantage that we have stressed in an earlier publication:[8] the plasma creatinine value alone can serve as an index of renal failure. This is contrary to what is the case with blood urea concentration. Thus, plasma creatinine determination is valuable both as a screening test and in following the course of renal failure, as changes in the plasma creatinine concentration will give a satisfactory picture of the situation.

As mentioned above, the chemical determination of plasma creatinine is the weakness of the method. But, contrary to what is believed, this weakness is not so great that it cannot be overcome by simple means. Almost all discrepancies concerning endogenous creatinine values depend on differences in the method used. Small deviations from the procedure (which is described below) will be unimportant in clinical medicine. We think we have reason to state that our procedure gives results as close to the factual as possible. As is well known, the color reaction given by alkaline picrate is not specific for creatinine, but is given by several plasma components. As shown by one of us,[6] both glucose and acetone give this reaction, and there are also other substances. In clinical work one can overlook this source of error, except in cases where there are distinctly raised blood sugar values or acetonemia, conditions that greatly enhance the development of the color reaction.

Creatinine may be determined by two different color reactions, viz., by the aid of alkaline picrate and by the 3,5-dinitrobenzoate method. According to Mandel and Jones,[9] the last method is no more specific than the alkaline picrate method, and is less practical. We have ourselves had no experience with this latter method, and in the following only the alkaline picrate reaction of Jaffé will be discussed.

The original method has been altered several times without resulting in improvement. Bonsnes and Taussky[3] examined the method and found the color developed in the Jaffé reaction independent of the picric acid concentration; a weaker picric acid solution will give the same results as the original saturated picric acid. We have ourselves made use of both the weaker picric acid of Bonsnes and Taussky and the modification of Peters,[11] and have found that neither of these modifications gives any advantage. We are therefore using saturated picric acid.

Bonsnes and Taussky introduced a modification of the NaOH concentration, using 3 ml. of the unknown, 1 ml. of a 0.04 M solution of picric acid, and 1 ml. of 0.75 N NaOH. We have compared their method with the original one and found it no better. We therefore use the original Folin method (2 volumes of the unknown plus 1 volume of alkaline picrate, prepared immediately before use from 5 volumes of saturated picric acid solution and 1 volume of 10 per cent NaOH).

It is unnecessary to use freshly prepared solutions of picric acid, in spite of the fact that "old" solutions of picric acid give a deeper color with sodium hydroxide than freshly prepared ones. This is due to the circumstance that the deepening of the color when using "old" solutions of picric acid will be the same both in the blank and in the samples to be tested. This was pointed out by Owen et al.,[10] but we have made the same observations ourselves.

Opinion differs concerning the use of wave length and calibration curves. Without doubt, the greatest optical density is got at a wave length of about 500 mμ, but at this wave length the calibration curve is not linear. As the wave length increases, the relationship between the optical density and the concentration of creatinine becomes more linear, and at about 515 or 520 mμ the relationship is linear, at least at lower concentrations of creatinine. On the other hand, the optical density will be less at higher wave lengths. One therefore has to choose between high optical density and linearity of the calibration curve. We have chosen a wave length of 500 mμ for the Coleman Junior spectrophotometer. In daily routine work we have made use of two Klett-Summerson colorimeters (green filters), and have got very good conformity of the creatinine values. Of course, a calibration curve has to be worked out for each colorimeter, and the curve has to be checked frequently. However, if the procedure on every determination is the same, the calibration curve also will be the same.

It has been shown that the temperature of the solutions prepared for colorimetry is of great importance, as the color increases with increasing temperature.[7] We use 23° C., as this is the average temperature in our laboratory. All glassware used for the Jaffé reaction is kept in a water bath of this temperature, from the addition of alkaline picrate until the reading is finished. The calibration curve also has to be worked out at this same temperature.

The color has to be read at a constant time interval after the addition of alkaline picrate. In aqueous solutions of creatinine and in diluted normal urines the color will be fully developed after 10 minutes. In plasma filtrates, however, the color will darken for at least an hour or more (see below).

Whereas the determination of creatinine in the urine is very simple, there are several difficulties concerning the determination in plasma or blood, due to such circumstances as the unspecificity of the Jaffé reaction and the protein precipitation. It is mostly held that plasma (or serum) is to be preferred to blood, as blood cells are supposed to contain chromogens which will give too high concentrations of creatinine. In our hands, full blood has given about the same values as plasma if the color is read after 10 minutes; nevertheless, we always make use of plasma with heparin as anticoagulant.

Several methods for the precipitation of plasma proteins have been proposed, most of them using sodium tungstate and sulfuric acid in different

concentrations. Brod and Sirota [4] recommended a modification of the Folin and Wu precipitation (1 volume of plasma, 1 volume of water, 1 volume of a 5% solution of sodium tungstate, 1 volume of 0.66 N sulfuric acid). We have found this modification very satisfactory. The advantage is a small dilution of plasma (1:4); every milliliter of filtrate thus contains relatively much creatinine. This method also gives a very good recovery percentage; Brod and Sirota themselves recovered 100.2% of added creatinine, a result which was confirmed in our laboratory [7] and by Owen et al.[10]

It was mentioned above that the color reaction of aqueous solutions of creatinine and of diluted normal urines is fully developed after 10 minutes. The color increase of plasma filtrates after 10 minutes is probably due to other chromogens than creatinine. This can be seen from the fact that after treatment with Lloyd's reagent (for estimation of true creatinine) there is no increase in color after 10 minutes. Roscoe,[12] however, maintained that the color due to creatinine in a Brod and Sirota filtrate is not fully developed before 60 minutes because of the strongly acid reaction (pH of about 1.5 to 1.6). We have confirmed this, as we have found that the color of creatinine buffer solutions with a pH of 2.0 is fully developed after 10 minutes, whereas the complete color development in solutions with a pH of 1.5 takes a little more time. The difference is, however, very small and of no significance. In a comparison between the creatinine values of Brod and Sirota filtrates and those of a more "neutral" filtrate (using 0.33 N sulfuric acid instead of the 0.66 N sulfuric acid of Brod and Sirota) with a pH of about 4.0, we found the ratio "acid filtrate"/"neutral filtrate" equal to 1.004 (43 experiments). We have therefore continued to make use of the Brod and Sirota precipitation, and we read the color after exactly 10 minutes, as we do also for diluted urines.

Determined in this manner, the plasma creatinine values in normals will be found around 0.9 to 1.0 mg./100 ml. We do not deny that small deviations from the procedure outlined above may give equally good results. The most important point of all is that the procedure is standardized and that the reaction is always performed in exactly the same manner. We have been very well satisfied with the method. We find proof in the fact that daily determinations of creatinine values in the single normal individual show no variations for weeks, a fact which until now has been insufficiently appreciated.

The normal creatinine clearance estimated according to this method is about 100 ml./minute, with a range between 70 and 130 ml./minute. As a rule, however, it is unnecessary to perform a complete clearance; a plasma creatinine determination will suffice, as there is an inverse relationship between creatinine clearance and plasma creatinine concentration. In normals we have almost never found plasma creatinine above 1.3 mg./100 ml., and we regard this value as the upper normal limit. Of course, renal function may be reduced in spite of a plasma creatinine below 1.3 mg./100

ml. If an individual normally has a plasma creatinine value of 0.80 mg./100 ml., a concentration of 1.20 mg./100 ml. will signify a reduced renal function. However, in such a case one will get no more information out of a complete clearance determination, as the clearance values also are subject to wide variations. In our hands the creatinine clearance values are definitely pathologic when below 60 ml./minute, and at such a reduced renal function, plasma creatinine will be above the upper normal limit of 1.3 mg./100 ml.

There is one practical point that may serve as a control when doing a complete creatinine clearance test. We have stated that in renal failure the plasma creatinine level corresponds fairly to the degree of renal damage.[2] The correctness of this statement can be seen from the fact that the product of the plasma creatinine concentration (in mg./100 ml.) and the creatinine clearance (in ml./minute) is quite constant and rarely will be found very far from 100, i.e., the average normal creatinine clearance value. If the plasma creatinine concentration is raised to 2 mg./100 ml. (about double normal), the clearance will be found around 50 ml./minute (half normal), etc. We have found that deviations from this rule usually are due to errors in urine collections or in creatinine determinations.

Finally, we wish to point out that the method outlined above is one suitable for daily clinical work. For scientific work one may have to make use of methods which more exactly determine true plasma creatinine, e.g., by the aid of Lloyd's reagent as shown by Hare,[5] ourselves [8] or Owen et al.[10]

Summary

Reasons are brought forth for our changing attitude during the last few years toward renal functional tests in clinical medicine. Whereas in earlier days we often made use of several clearance tests simultaneously for the evaluation of renal function, our present practice is most often only a determination of the plasma creatinine concentration. The usefulness of this practice rests upon the reliability of the method for creatinine determination. Consequently, the method adopted by us is discussed above in necessary detail. If this procedure is followed generally, creatinine values, at any place and at any time, will be uniformly comparable.

Summario in Interlingua

Duo tests de clearance renal es hodie de importantia concurrente in le medicina clinic: le test del clearance de urea e le test del clearance de creatinina. Le clearance de urea es de grande interesse physiologic, sed le mesme es etiam ver pro le clearance de creatinina. Un disavantage del test del clearance de urea es le facto que le concentration intraplasmatic del urea depende del quantitate de proteina ingerite e in plus que le clearance de urea varia con le diurese, de maniera que duo formulas es requirite pro le calculation. Un de iste formulas labora con un signo de radice quadrate e es comprendite per pauc clinicos. Quanto a creatinina—in iste articulo designate como "substantias Jaffé-positive"—su concentration intraplasmatic es

remarcabilemente constante durante prolongate periodos de tempore. Deviationes de plus que 0,1 mg per 100 ml es generalmente indicative de errores technic. Un altere facto interessante es le constantia del diurne excretion de creatinina in le urina. Le valor de iste excretion—providite que su determination chimic es correctemente executate—pote esser usate como controlo del collection de urina. Le disavantage del test a creatinina es que il non existe un specific methodo pro le determination de iste substantia. Sed Hare e le autores del presente articulo ha demonstrate que ver creatinina pote esser determinate per medio del reagente de Lloyd. Nonobstante, le uso de iste methodo non es necesse in le routine quotidian excepte in casos de diabete mellite, proque augmentate quantitates de glucosa e acetona age como "substantias Jaffé-positive."

Quanto al procedimento chimic, le sequente detalios es discutite e sublineate:

1. Concentration de acido picride in le methodo de Jaffé: Esseva usate un solution saturate. Modificationes de isto es discutite. Illos non presentava avantages. (Etiam le methodo a 3,5-dinitrobenzoato non presentava ulle avantage.)

2. Concentration de NaOH: Le methodo original de Folin esseva usate. Le modificationes de Bonsnes e Taussky presentava nulle avantage.

3. Longitude del unda e curvas de calibration: Esseva usate undas a 500 m de longitude pro le spectrophotometro de Coleman (Filio). Isto resulta in un plus alte densitate optic que undas a longitudes de 515 o 520 m. Del altere latere, le curva a 500 m non es completemente linear. Sed on debe esser satisfacite del un o del altere de iste meritos. Colorimetros de Klett-Summerson con filtros verde produceva valores de creatinina de bon conformitate. Curvas de calibration debe esser elaborate individualmente pro cata apparato. Il es etiam necesse verificar los a intervallos. Le temperatura debe esser constante. Le temperatura al tempore del calibration del curvas debe esser identic con le temperatura al tempore del determinationes. In le studios hic reportate un temperatura de 23 C. esseva usate.

4. Tempore del lectura del instrumentos: Le lecturas esseva facite post 10 minutas tanto pro le filtrato de urina como etiam pro le filtrato plasmatic. Le rationes pro iste procedimento es discutite in detalio.

5. Precipitation de proteina: Esseva usate le modification de Brod e Sirota. Le rationes pro iste procedimento es discutite. Illo da un dilution plasmatic de solmente 1:4 e un excellente recuperation (100 pro cento).

Per medio de iste procedimento, le normas del concentration intraplasmatic de creatinina esseva trovate in le vicinitate de 0,9 a 1,0 mg per 100 ml e non supra 1,3 mg per 100 ml. Le mesme valores esseva constatate pro sanguine. Le clearance de creatinina es in le vicinitate de 100 ml per minuta e varia inter 70 e 130 ml per minuta. Il es a notar que como mesura de lesion renal le determination del concentration intraplasmatic de creatinina es sufficiente. Le producto del valor de iste concentration con le valor del clearance de creatinina exprimite in ml per minuta fluctua in le vicinitate de 100. Su fluctuation non es multo plus extreme que le fluctuation del clearance mesme. Assi un concentration intraplasmatic de circa 2 mg de creatinina per 100 ml es usualmente incontrate quando le clearance de creatinina es in le vicinitate de 50 ml per minuta; circa 4 mg de creatinina intraplasmatic per 100 ml es incontrate quando le clearance es 25 ml per minuta; etc.

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BENIGN ESSENTIAL HYPERTENSION: FOLLOW-UP OF 100 PATIENTS UNDER OBSERVATION FOR FROM 18 TO 34 YEARS *

By Alex. M. Burgess, M.D., F.A.C.P., *Providence, Rhode Island*

This is a report on the condition of 100 patients seen in private practice between the years 1920 and 1936. All had systolic pressures of at least 180 mm. Hg or diastolic pressures of 100 mm. Hg or higher when first observed, and had survived for at least eight years. These were the first hundred individuals seen in the practice of the writer to whom these criteria were applicable. The group was reported in 1946,[1] and the present communication summarizes their condition in the fall of 1954.

A number of studies of prognosis in patients with essential hypertension have been published,[2, 3, 4] although in no two of them are the same criteria used as to what should be considered *essential* hypertension, and in but few of them is the final prognosis as to length of life considered. Nevertheless, there appears to be a general agreement that there is a type of long-standing, nonprogressive hypertension without symptoms, in which neither the use of hypotensive drugs, so-called, nor surgical interference is warranted. Most

Table 1

100 PATIENTS
74 Dead 18 Alive 8 Unreported
Average life 2.7 yrs. below expectancy

Age 50 Years or Less—32
17 Dead 13 Alive 2 Unreported
Average life 7.6 yrs. below expectancy

Age Over 50 Years—68
55 Dead 7 Alive 6 Unreported
Average life 1.2 yrs. beyond expectancy

of the authors of these reports are in hospital practice and see patients, the majority of whom are sick enough to have been referred to them. What may not be so clearly realized is that the benign type of hypertension with relatively high systolic pressure, which does not show retinal, renal or cardiac damage in its early stages, that type which some observers agree does not require any treatment, is *the common type.*

Since only those who had survived at least eight years are included, it is believed progressive, so-called "malignant" hypertension is eliminated. It will be noted in table 1 that the average individual in this whole group has lived to within 2.7 years of his life expectancy.

Table 2 shows a graph on which are indicated the life spans of the 100 individuals studied. The normal average expectancy of life as contained in

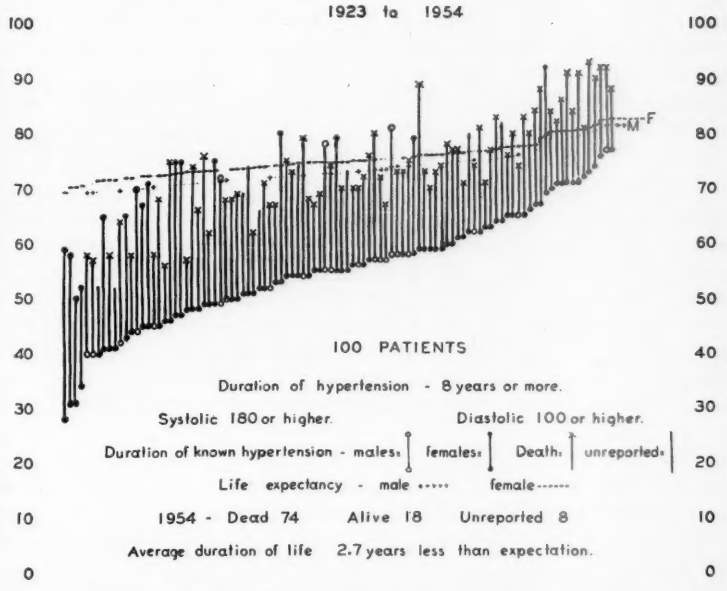
* Received for publication May 17, 1955.

insurance tables [5] is also given. It is clear that the majority of the older patients lived to beyond their expectancy. It is of interest that five patients had systolic pressures of over 300 mm. Hg on one or more occasions, and that all five lived well beyond their life expectancies. The height of the systolic pressure appeared to be of little significance in comparison with the diastolic.

In several of these patients extreme hypertension noted early in life has become less marked with the years. In some this result has been due to

TABLE 2

EXCESSIVE HYPERTENSION



obvious coronary disease, but in others no definite cause can be assigned, unless possibly an easing of the tensions of life.

In considering the findings in the whole group, one gains certain impressions which are perhaps of value. As is well known, single observations of elevation of the systolic or diastolic pressures are of little significance compared with sustained elevation, particularly of the diastolic pressure.

The commonest cause of death was cardiac, the next commonest cerebral, and in several damage to both systems occurred before death supervened.

It must be remembered that although the benign type of hypertension, such as is described in this communication, is usually a completely symptom-

less condition, anxiety regarding hypertension—hypertensophobia, if you choose—is most distressing. As one of my colleagues once put it: "The blood pressure apparatus ranks next to the internal combustion engine in the list of inventions that have been harmful to the human race." With the availability of the newer medications which accomplish blood pressure reduction, which certainly have their place, there is an increasing tendency to call the patient's attention to his blood pressure, to increase his anxiety regarding this condition, and then to apply those newer medications, which are not without their disadvantages, when the situation would in many instances have been much better had the hypertension been left unmentioned and untreated. Among the 100 patients here reported, only a few were aware of their hypertension, and the harm that this awareness did to some of them was obvious. None had symptoms that could definitely be attributed to the hypertension. While there is no reason why a person with essential hypertension should not develop the "malignant" condition in the same manner as may any other individual, it is notable that none of these patients did so.

Summary and Conclusions

1. One hundred persons with essential hypertension were observed during the years 1923 to 1954 (inclusive). All of these had shown a systolic pressure of 180 mm. Hg or higher, or a diastolic pressure of 100 mm. Hg or higher, and had remained in good health for eight years before being included in the series. They were otherwise unselected.

2. By July 1, 1954, 74 had died, 18 were alive and well, and eight could not be traced. When the last report of those who could not be traced was counted as the end of their lives, the average individual of the whole group had lived to within 2.7 years of his life expectancy, as shown in life insurance tables.

3. Thirty-two patients were 50 years of age or younger when first observed to have hypertension. The youngest was 28 years. Of this group 17 had died, 13 were alive, and two could not be traced. The average individual had, at the time of this report, lived to within 7.6 years of his life expectancy.

4. Sixty-eight patients were over 50 years of age when first found to be hypertensive. Of this group 55 had died, seven were alive, and six could not be traced. The average individual of the group had lived 1.2 years *beyond* his life expectancy.

5. None of the patients had symptoms directly attributable to hypertension.

Some dizziness and occasional headaches were mentioned by the older group, in about the same proportion as occurs in others of the same age. Systolic pressures of over 300 mm. Hg, as was seen in five patients, did not appear to cause any symptoms.

6. No patients developed malignant hypertension.

7. Although the series is too small to allow definite conclusions or to be of statistical value, as it represents the experience of the author in private practice over a period of years and is to some extent based on the observations of neighbors, friends and relatives, many of whom have been seen frequently year in and year out, it has caused the formulation of certain definite impressions which may be of some interest.

8. Essential hypertension of long duration is a non-progressive, benign condition which, in the absence of cardiac, retinal or renal damage, is compatible with a duration of life up to normal expectancy in individuals over 50 and in many who are under that age.

9. It is the commonest type of hypertension seen in private practice.

10. The anxiety that is associated with the knowledge on the part of a patient that his blood pressure is high may be very distressing; therefore, it is usually wrong to direct the patient's attention to the condition.

11. Unless or until the patient shows cardiac, retinal or renal damage to be beginning, surgery is certainly not indicated, and the temptation to use the modern hypotensive drugs should be resisted.

12. Early malignant hypertension may be indistinguishable at first from the benign condition which I have described, and frequent observation is advisable in such instances until the situation is clear.

SUMMARIO IN INTERLINGUA

Le presente studio esseva completate in 1954. Illo es basate super datos colligite in le practica private del autor. Es includite in illo le prime 100 patientes qui, primo vidite inter 1920 e 1936, habeva a ille tempore un pression systolic de al minus 180 mm Hg e un pression diastolic de al minus 100 mm Hg, e qui, in plus, superviveva pro al minus 8 annos. In julio 1954, 74 habeva morite; 18 viveva e se trovava ben; e 8 non essava traciabile. Alora le durantia median del vita de omne le individuos includite in le gruppo esseva—secundo le indicationes de tabulas de assecurantia—2,7 annos infra le probabilitate statistic. Trenta-duo del patientes habeva habite etates de 50 annos o minus quando lor hypertension esseva primo recognoscite. In 1954, le durantia median del vita de iste 32 individuos esseva 7,6 annos infra le probabilitate statistic. Sexanta-octo del patientes habeva habite etates de 50 annos o plus quando lor hypertension esseva primo recognoscite. In 1954, le durantia median del vita de iste 68 individuos esseva 1,2 annos *supra* le probabilitate statistic. Cinque patientes habeva habite—a un o plure tempores—pressiones systolic de plus que 300 mm Hg. Le vita de omne iste 5 patientes durava ultra le probabilitate statistic. Nulle del 100 patientes disveloppava maligne hypertension. Le elevation del pression diastolic esseva clarmente un plus serie consideration que le elevation del pression systolic. Iste benigne e non-progressive forma de hypertension es le forma vidite le plus communmente in practicas private. Si nulle lesion cardiac, retinal, o renal es manifeste, nulle tractamento es indicate, e le patiente se trova melio si ille non es informate de su condition hypertensive. Le majoritate de iste patientes mori finalmente per morbo cardiac. Al tempore de lor prime visita, iste condition pote esser nondifferentiabile ab hypertension maligne in un stadio precoce. In tal casos frequente observationes es a recommendar usque le situation es clar. Iste typo de hypertension pote exister in certe individuos infra le etate de 50 annos usque al fin de un duration de vita normal. In le caso de individuos con etates de supra 50 annos, un duration de vita normal es le regula.

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CHLORPROMAZINE (THORAZINE) HEPATITIS: REPORT OF THREE CASES *

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CHLORPROMAZINE HCl is a 10-(γ-dimethylaminopropyl)-2-chlorophenothiazine HCl introduced in France and England and, more recently, in the United States under the trade name Thorazine, for the treatment of psychiatric disorders, especially agitated and depressed states, acute and chronic alcoholism, nausea and vomiting of diverse etiology, and hiccups, and for the relief of pain as a potentiator of opiates, hypnotics and anesthetics.[1-7] Its use has increased tremendously in the last few months, particularly as a tranquilizer. As of March 1, 1955, it was estimated that Thorazine has been used in the United States in over 2,000,000 patients.[7]

Side effects following the use of chlorpromazine, which have been reported as minimal, consist primarily of drowsiness, dryness of the mouth, pyrosis, nasal congestion, some constipation, miosis, mild hypotension, tachycardia, ataxia and urticaria.[3, 4, 6, 7] However, serious reactions, hepatic in origin, may occur early in the course of therapy with this drug. Reports of hepatitis have already appeared,[8-13] and we wish to record our experience with three such cases.

CASE REPORTS

Case 1. A 65 year old white male had been under our care since October, 1947, because of recurrent bronchitis, mild angina and frequent bouts of mental depression. When seen in the office on January 3, 1955, the patient complained of anorexia, tremor and "shaking within the body," mental depression, exhaustion and insomnia. On questioning, the patient appeared to be worried about his business affairs. Physical examination was noninformative, and urinalysis, hemoglobin and blood urea nitrogen were found to be within normal limits. He was placed on chlorpromazine HCl (Thorazine), 25.0 mg. three times a day, with considerable improvement. The drug was continued until January 22, when the patient developed chills, fever and nausea. The temperature reached 103° F., but examination failed to reveal any gross abnormalities. Tetracycline, 250.0 mg. every six hours, was ordered. Daily chills and fever continued, and on January 24 the pharynx was found to be injected and a few râles were detected in the left base.

The patient was admitted to the Chester Hospital with a temperature of 101.8° F., pulse of 70 to 90 per minute, and respirations of 20 per minute. During the first night of hospitalization the patient complained of chilliness and sweating, and on the morning of January 26 the temperature rose to 104° F. That evening it dropped to 98.2° F., and thereafter it ranged from 97° F. to 99° F. (rectally), with an occasional rise to 100° F. Routine laboratory studies are shown in table 1. X-ray of the chest and electrocardiogram were reported as normal. An adequate fluid intake and 600,000 units of crystalline penicillin were ordered every six hours.

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On January 26 the patient's complaints were weakness and anorexia; jaundice was then noted, but neither the liver nor the spleen was palpable or tender, and there was no adenopathy. The results of liver function tests are shown in table 1. The patient was placed on a high protein, high carbohydrate diet, and was given methionine, 1 gm. three times a day, a high vitamin B intake and diphenhydramine (Benadryl), 25 mg. three times a day. Steroid therapy (cortisone, ACTH) was considered inadvisable in view of the patient's psychiatric background. On January 29 the jaundice increased and pruritus became annoying. The stools were acholic and the urine contained bile. The liver was then palpated two fingerbreadths below

TABLE 1

Laboratory Tests in Case 1

	1/25/55	1/26	1/28	1/31	2/2	2/8	2/16	2/18	2/23	3/16	3/31
Hematocrit Hemoglobin WBC Polymorphonuclear leukocytes Lymphocytes Eosinophiles Monocytes	45 14.6 4,600 65% 18% 16% 1%				10,500 69% 18% 12% 1%		11.8 9,500 57% 38% 5% 0				
Urine: Bile Urobilinogen		+3 0									
B.U.N.: mg./100 ml.	19										
Bilirubin: mg./100 ml. 1 min. 30 min.		3.2 4.5		6.6 9.8		2.2 3.5		0.8 1.7		0.04 0.9	
Cholesterol: mg./100 ml.			313		539	507	299		264	300	254
Alkal. phosphatase Bodansky units			4.3		6.8	23	24		20.6	11.0	6.8
Thymol turbidity units			1								
Cholest.-cephalin flocculation			24 h.0 48 h.0								
VDRL	Non-reactive										
Heterophil agglutination					0						
Duodenal drainage				Bile + Crystals 0							
Sed. rate corrected mm./hr.	34										
Coag. time Lee-White				4 min.							
Bleeding time				1′ 5″							
Prothrombin time: Patient Control			15 sec. 15 sec.	13 sec. 14 sec.							

the costal margin; it was soft but not tender. On January 30 a discrete papular eruption appeared on the trunk; it lasted five days, but its cause was undetermined.

On February 1 the appetite returned, despite further increase in jaundice; biliary drainage revealed the presence of bile which did not contain any crystals. An upper gastrointestinal x-ray study was negative for any organic lesion or extrinsic defect. No stones were seen in the region of the gall-bladder. On February 3 a needle liver biopsy was done through the right eighth intercostal space; the histopathology report was: "The sections disclosed inspissated bile plugging tiny canaliculi. Of interest is the presence of focal collections of polymorphonuclear leukocytes and lymphocytes which are located predominantly in the periportal areas. *Comment:*

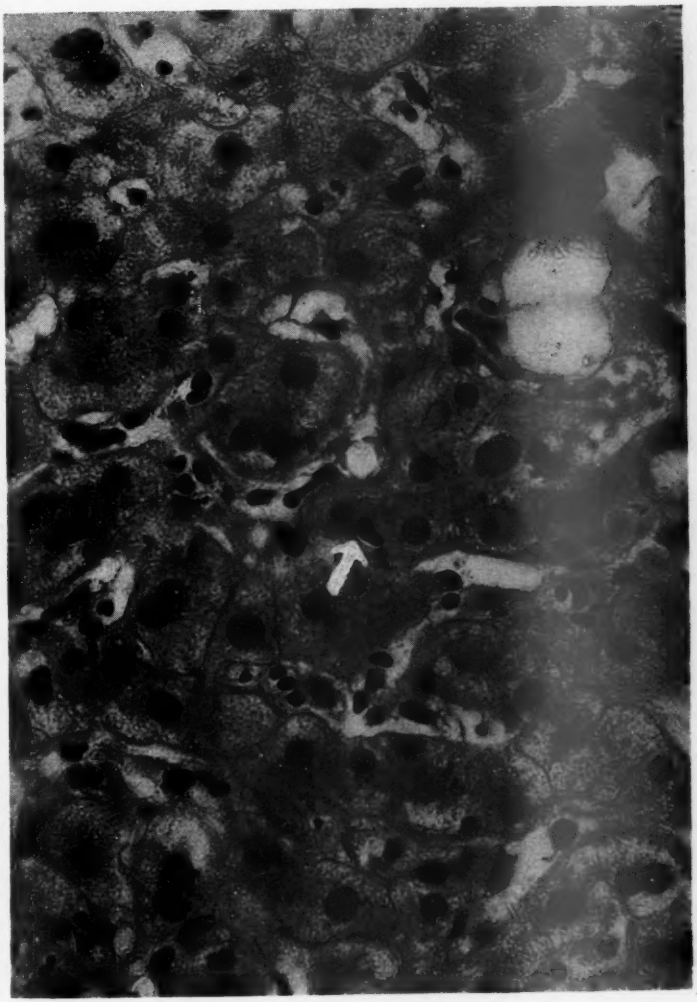

FIG. 1. *Case 1.* Liver biopsy. Arrow points to inspissated bile. A moderate lymphocytic infiltrate is present.

The process is deemed compatible with 'Thorazine hepatitis.' The significance of the polynuclears is not ascertainable."

On February 5 the jaundice began to recede but the pruritus persisted for two more weeks. The stools and urine returned to normal color on February 13. On February 21 an intravenous cholografin study revealed normal hepatic and common bile ducts and a normally functioning gall-bladder without evidence of stones.

The patient was discharged markedly improved on February 22, 1955. Gradual resumption of activities with steady gain in strength took place; follow-up studies are given in table 1.

Case 2. A 73 year old white female was admitted to the Chester Hospital on February 3, 1955, because of nausea, vomiting, abdominal pain, fever and jaundice. She had had moderately severe Parkinson's disease since 1915, and had lately received trihexyphenidyl (Artane), 3.0 mg. three times a day, without much improvement. On January 10, 1955, following a fall at home, she had sustained fractures of the left clavicle and several ribs. This was followed by considerable mental depression, until January 15, when she suddenly became disoriented as to time and place, and developed periods of agitation. She was then seen by one of us (F. R.), who was impressed by the possible causative rôle of prior medication on the patient's psychosis. All drugs were stopped, and the patient was placed on Thorazine, 25.0 mg. three times a day, with a prompt return to normalcy. The drug was continued until January 30, when the patient suddenly developed a fever of 101° F., anorexia and recurrence of mental depression. On February 1 she complained of epigastric pain associated with dark urine and light-colored stools. Next day she became definitely jaundiced and was referred to the Chester Hospital for study. During the first few days of hospitalization her temperature ranged between 99° and 99.8° F.; pulse, from 60 to 90 per minute; respirations, 20 per minute. Anorexia and severe pain in the right upper quadrant of the abdomen were the outstanding complaints. The stools were clay-colored and the urine contained bile; examination revealed a tender mass in the region of the gall-bladder extending 3 to 4 cm. below the right costal margin; it moved with respiration and felt quite firm. We could not be certain whether we were dealing with a distended gall-bladder or an enlarged lobe of the liver. Pertinent laboratory studies are shown in table 2. Although the history of ingestion of Thorazine pointed to the probable existence of drug hepatitis, the laboratory tests, together with the severe pain and the palpable tender mass which persisted during the first week of hospitalization, raised the question of the possible existence of extrahepatic obstruction, either stone or malignancy. Attempts at duodenal aspiration were unsuccessful, and a flat plate of the abdomen failed to reveal any positive stones in the gall-bladder area. Because the patient's condition deteriorated, it was considered advisable to request a surgical consultation. Dr. Palmer deFuria agreed that extrahepatic obstructive disease should be excluded by surgical exploration. The latter was carried out on February 12; the gall-bladder was found to be normal in appearance, with a thin wall, but it was surrounded by many recent thin, veiled adhesions. No stones were felt in it or in the cystic duct, which was small. The common bile duct was definitely larger than is usually found, but its walls were thin. On needle aspiration, dark, viscid bile was obtained from the common duct. The pancreas appeared to be normal in consistency. The liver was definitely enlarged; it had blunt edges and was green-gray in color, and its left lobe was obviously the tender mass that had been palpated prior to surgery. The common bile duct was opened and thoroughly explored; it was found to be patent and without any stones. A T-tube was placed in it for drainage. A biopsy of the liver was obtained with a Vim-Silverman needle; microscopic examination revealed the following: "Some of the smaller bile canaliculi are filled with inspissated bile. Occasional hepatic parenchymal cells contain pigment. There is no evidence of malignancy. Periportal

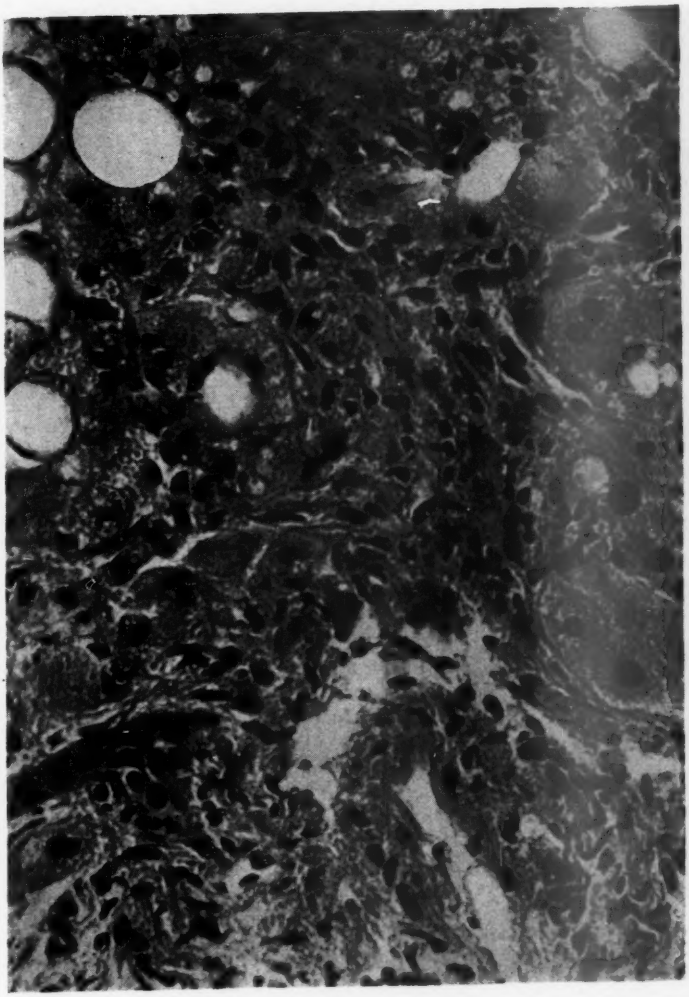

FIG. 2. *Case 2.* Liver biopsy. Periportal area shows minimal fibrosis and lymphocytic and polymorphonuclear leukocytic reaction.

areas show only minimal fibrosis. *Comment:* The process is compatible with obstructive jaundice."

Following operation the patient's jaundice decreased very rapidly and with supportive treatment she made an uneventful recovery. She was discharged, considerably improved, on February 25, twenty-three days after admission. At home the patient continued to do well.

The results of follow-up liver function tests are shown in table 2.

TABLE 2
Laboratory Studies in Case 2

	2/4/55	2/8	2/17	2/23	3/16	3/31
Hematocrit	37					
Hemoglobin	11.4					
WBC	9,000					
Polymorphonuclear leukocytes	54%					
Lymphocytes	36%					
Eosinophiles	5%					
Monocytes	5%					
Urine: Bile	4+			0		
Urobilinogen	+(Undil.)			+(1–10)		
Bilirubin: mg./100 ml.						
1 min.	4.8	9.5	3.2	1.4	0.65	
30 min.	10.3	14	5.5	2.3	1.25	
Cholesterol: mg./100 ml.	353		300	231	316	244
Alkal. phosphatase Bodansky units	21.9		12.0	15.1	13.2	7.4
Thymol turbidity units	1.5					
Cholest.-cephalin flocculation	48 h.+2					
VDRL	Non-reactive					
Sed. rate corrected mm./hr.	36					
Coag. time Lee-White		10′ 35″				
Bleeding time		1′ 10″				
Prothrombin time:						
Patient	16 sec.					
Control	15 sec.					

Case 3. A 68 year old white female was admitted to the Chester Hospital on January 26, 1955, because of jaundice and pruritus which had been present for the previous three weeks but was then receding. The patient had had diabetes for about 15 years; it had been fairly well controlled by means of diet and 35 units of NPH insulin, plus 5 units of crystalline zinc insulin daily. In September, 1954, she had developed bouts of vomiting which persisted for about one-half day and recurred about once monthly. Because of the increasing severity of these episodes, on December 4, 1954, her family physician placed her on chlorpromazine, 25.0 mg. three times a day, which she continued until December 29, when the drug was stopped. On December 22, 1954, the patient developed a fever of 102° F., malaise, vague abdominal pains and weakness. Examination by her physician failed to reveal the cause for

TABLE 3
Laboratory Tests in Case 3

	1/27/55	1/28	1/31	2/1	2/2	2/4	2/7	2/9	2/11	2/14	2/18	2/23	2/25	6/2
Hemoglobin WBC Polymorphonuclear leukocytes Lymphocytes Eosinophiles Monocytes	6.8 7,600 69% 28% 2% 1%													
Urine: Bile Urobilinogen	Sl. trace +1:10						Sl. trace 0						0 0	
B.U.N.: mg./100 ml.			50		58		67						55	
Bilirubin: mg./100 ml. 1 min. 30 min.	1.2 2.4				1.1 2.0			0.65 1.3			0.275* 0.42	0.21* 0.48		
Cholesterol: mg./100 ml. Cholesterol esters "		1,768		1,459				1,375			1040* 656	806* 410		253*—
Phospholipids: mg./100 ml.											44.0*	40.4*		14.9*
Total fatty acids: mEq./L.											43.0*	39.7*		11.5*
Alkal. phosphatase Bodansky units	7.2					37.6		40.3		51.4			47.8	6.3

TABLE 3—*Continued*

	1/27/55	1/28	1/31	2/1	2/2	2/4	2/7	2/9	2/11	2/14	2/18	2/23	2/25	6/2
Thymol turbidity units											2.2* 2.2	2.1* 2.2		2.1*
Thymol flocculation											0* 0	1+* 1+		0* 0
Cholest.-cephalin flocculation	1+							±	±		0* 0	1+* 1+		0* 0*
Zinc sulfate turb.											0.8*	1.8*		1.1*
VDRL	Non-reactive													
Coag. time Lee-White										7′ 20″				
Bleeding time										1′ 50″				
Prothrombin time: Patient Control									13 14	13 13				
B.S.P. ret. 30 min. 2 mg./kilo.											Less than 5%			

* Tests performed in Pepper Laboratory of University of Pennsylvania Hospital, Philadelphia, through kindness of Dr. J. G. Reinhold.

these symptoms, but during the following week the patient noted the gradual onset of jaundice. This increased in severity and, in the absence of any abnormal abdominal findings, the attending physician suspected the icterus to be the result of Thorazine. Hospitalization was recommended but this was not carried out until three weeks after the onset of the jaundice, when it was already subsiding. Her past medical history revealed three hospital admissions, in 1950 and 1951, for regulation of her diabetes; in 1950 her serum cholesterol had been recorded as 108.0 mg.%. In January, 1954, she was re-admitted to the Chester Hospital because of dependent edema and pyelonephritis complicating her diabetes. The possibility of Kimmelstiel-Wilson disease was considered but not established. At that time her serum cholesterol was found to be 240 mg.%. A moderately severe anemia was present.

Following the present admission, her temperature remained normal; there were slight icterus and evidence of itching; there was considerable pallor of the conjunctivae and mucous membranes; the heart was regular (rate, 80/minute); the lungs were clear; the liver edge was palpable two fingerbreadths below the right costal margin and was not tender; the spleen was not palpable. Liver function studies are shown in table 3. Urinalysis showed definite fixation of specific gravity between 1.005 and 1.010; there was a persistent slight trace of albumin and pyuria, with the recovery of *Escherichia coli* and *Aerobacter aerogenes* organisms from the urine on several occasions. On admission the hemoglobin was 6.8 mg. and the hematocrit 23 vol. %; the blood urea nitrogen was persistently elevated, ranging from 50 mg. to 67 mg.%. The serum proteins were definitely low: on January 27, total protein was 5.3 gm.; albumin, 2.5 gm.; globulin, 2.8 gm.; on February 18,* total protein was 5.2 gm.; albumin, 1.5 gm.; alpha$_1$ globulin, 0.50 gm.; alpha$_2$ globulin, 1.24 gm.; beta globulin, 0.96 mg.; gamma globulin, 0.67 gm. (The pattern shows marked elevation in alpha$_2$ globulin and some elevation of the alpha$_1$ globulin, with significant decrease in the albumin and gamma globulin fractions.) On February 23* the total protein was 5.2 gm.; albumin, 2.02 gm.; alpha$_1$ globulin, 0.49 gm.; alpha$_2$ globulin, 0.93 gm.; beta globulin, 1.06 gm.; gamma globulin, 0.71 gm. (abnormality lessened, but gamma globulin remains low). The blood sugar was very difficult to control and, despite increasing doses of insulin, stayed around 250.0 mg./100 ml. (fasting). During the patient's hospitalization the following studies were carried out: An upper gastrointestinal x-ray series was within normal limits. A gall-bladder dye study (on February 9) revealed normal function and no evidence of stones in the gall-bladder or ducts. A skull x-ray was within normal limits. A basal metabolic rate (February 18) was plus 7. A needle liver biopsy was done through the right eighth intercostal space on February 16; the microscopic study was reported as follows: "Periportal areas show moderate fibrosis and contain scattered polys and lymphocytes. Here and there the liver nuclei show hyperchromatism, while elsewhere they show vacuolization. Some portions of the tissue show bile in the smaller biliary canaliculi. *Comment:* The process is deemed compatible with 'Thorazine hepatitis.'"

The jaundice cleared on February 10. The patient was treated intensively with antibiotics in an attempt to control the renal infection and was given blood transfusions, with some improvement in the anemia; the diabetes was controlled by diet and large doses of insulin, with an occasional spilling of sugar in the urine. She was discharged improved on March 3, 1955. Follow-up studies are shown in table 3.

Discussion

Jaundice was noted by Winkelman [4] as an incidental finding in three patients of his series of 142 that had been treated with chlorpromazine.

*Electrophoresis of serum protein was performed through the kindness of Dr. J. G. Reinhold, of the Pepper Laboratory of the University of Pennsylvania Hospital, Philadelphia.

They had received the drug for from two to five weeks, and got well upon discontinuance of the medication. This author also quotes a similar experience of Harper in England. Lehman and Hanrahan [1] observed jaundice in three patients out of 71; these three had taken the drug for from two to four weeks. Azima and Ogle [12] encountered five cases of jaundice in 100 patients receiving the drug; Moyer et al.[6] reported one instance of icterus in more than 500 patients treated with this drug for nausea and vomiting, and Lemire and Mitchell [8] studied three cases of persistent jaundice in elderly patients receiving chlorpromazine (50 to 200 mg. daily) for from 15 to 32 days. One of the patients showed a transient eosinophilia (up to 17%). All three patients underwent laparotomy. Zatuchni and Miller [9] described in detail a case of jaundice that came to surgery without any cause being found for the obstruction portrayed by the liver function tests; liver biopsy revealed the presence of cholangiohepatitis, which was attributed to chlorpromazine. Van Ommen and Brown [10] reported three cases of jaundice due to this drug; two of the patients were operated upon, one four months after the onset of the disease, because malignancy could not be ruled out even though drug hepatitis had been suspected. Lastly, Moyer, Kinross-Wright and Finney [13] encountered one case of jaundice among 412 psychiatric patients treated with chlorpromazine, and saw this complication in several patients treated elsewhere.

It is difficult to estimate the incidence of jaundice in subjects treated with chlorpromazine; in institutionalized psychiatric patients, it has been reported in approximately 1%, usually appearing in the second to fourth week of treatment.[7]

Our three cases occurred in elderly individuals following ingestion of chloropromazine for about two weeks. The advanced age of our patients may be entirely coincidental; however, it raises the interesting possibility that the drug may be more toxic to such livers. Further study of this factor is indicated.

The illness in our cases began with fever, malaise and anorexia, and was followed by the rapid development of jaundice which, clinically and by laboratory tests, proved to be due to intrahepatic biliary stasis and obstruction. The hepatocellular function tests were normal, while the serum cholesterol and alkaline phosphatase were markedly elevated. The phosphatase remained high after the serum bilirubin and cholesterol had returned to normal. In this regard, we were much interested in the very high cholesterol values displayed by our case 3; in this instance, the hyperlipemia may have been due in part to the diabetes and renal disease that complicated the hepatitis. However, in 1954, in the absence of chlorpromazine hepatitis, the serum cholesterol was found to be 240 mg./100 ml. and on June 2, 1955, three months after discharge from the hospital the serum cholesterol was 253 mg./100 ml.

Liver biopsy is of value once the true etiology of the hepatitis is suspected

and the other causes of biliary obstruction are ruled out. The pathologic picture is that of cholestasis with plugging of the biliary canaliculi, and varying degrees of cellular infiltration of the portal spaces. Neutrophils, lymphocytes and especially eosinophils may be seen in abundance.[9-11] Our cases showed the characteristic picture, although eosinophils were not seen (figures 1, 2).

One of our patients (case 1) displayed a considerable peripheral eosinophilia, which has also been noted by others.[10, 11] This, together with the occurrence of fever and the lapse of two to four weeks before the onset of jaundice, has led to the assumption of the existence of an allergic or sensitization reaction as the mechanism for the jaundice induced by chlorpromazine. This type of hepatitis strongly resembles that due to other drugs, such as arsphenamine,[16] methyltestosterone [14] and thiouracil,[15] which has been ascribed to direct injury, altered bile viscosity, sensitization and metabolic changes in the liver.

Although Van Ommen and Brown recorded a slow response to steroids in one of their cases,[10] Gambescia [11] obtained excellent results with this therapeutic agent. The routine supportive régime employed in the treatment of jaundice due to other causes was instituted in our cases with good results.

Fortunately the jaundice cleared up rather promptly in our patients; however, it may last for months, as reported by Van Ommen and Brown[10] and Azima and Ogle.[12] Prompt recurrence of the jaundice upon resumption of the chlorpromazine therapy has also been reported.[11]

The most difficult problem presented by these patients is the differential diagnosis from extrahepatic biliary obstruction. From our experience with case 2 and that of others,[9, 10] it would seem advisable to postpone surgical exploration as long as possible whenever there is a history of ingestion of Thorazine, in the hope that the clinical picture will clarify itself through subsidence of the jaundice, if it is due to the drug. However, this may not always be feasible, especially since malignancy may also occur in patients taking chlorpromazine.

Because of the hazards involved and the seriousness of the hepatitis that may result, it is important that the use of chlorpromazine be strictly limited to those conditions where its benefits outweigh the risks.

Conclusions

1. Three cases of hepatitis produced by chlorpromazine are reported.
2. The jaundice occurred after two weeks of drug therapy; it was preceded by fever, malaise and anorexia, and in one case it was associated with pain and a tender mass in the right upper abdomen which led to surgery. The patients recovered in a few weeks.
3. The jaundice was associated with intrahepatic biliary stasis and

obstruction; the hepatocellular tests were normal, while the serum cholesterol and alkaline phosphatase were markedly elevated.

4. Eosinophilia was present in one patient. Liver biopsy supported the diagnosis of Thorazine hepatitis in all patients.

5. Because of the serious nature of this hepatic reaction, chlorpromazine should not be used promiscuously but should be reserved for those conditions where the benefits of the drug far outweigh the risks.

ACKNOWLEDGMENT

We wish to thank Dr. F. Skwirut, Chester, Pennsylvania, for making the medical record of case 3 available to us.

SUMMARIO IN INTERLINGUA

Es reportate tres casos de hepatitis adveniente post administration de chlorpromazina (Thorazina). Le morbo se declarava duo a tres septimanas post le uso del droga e comenciava per febre, frigido, e mal-esser, sequite per le rapide disveloppamento de ictero, feces acholic, e bilirubinuria. Essayos laboratorial demonstrava le presentia de ictero obstructive in le absentia de omne demonstrabile morbo del vias biliari extrahepatic. Eosinophilia esseva presente in un del patientes. Un del casos esseva operate proque il esseva impossibile disprovar le existentia de un causa chirurgic pro le ictero. In omne casos biopsias hepatic esseva executate per medio del agulia de Vim Silverman. Illos demonstrava le presentia de hepatitis con obstruction del canaliculos per bile inspissate.

Le ictero se clarificava post inter quatro e sex septimanas, sed le phosphatase alcalin e le cholesterol del sero persisteva a nivellos elevate durante considerabilemente plus longe periodos de tempore.

Nos conclude (1) que chlorpromazina non deberea esser usate promiscuemente sed deberea esser reservate pro uso in conditiones in que le effectos benefic del droga es plus importante que le seriose risco de hepatitis e (2) que le exploration chirurgic deberea esser postponite le plus longe possibile in omne casos de ictero con un historia de precedente ingestion de chlorpromazina.

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NEW DEVELOPMENTS IN THE DIAGNOSIS AND TREATMENT OF PERNICIOUS ANEMIA * †

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Criteria for the diagnosis of pernicious anemia must be reëvaluated in light of the changing pattern of this disease. The profound physical abnormalities and extreme hematologic aberrations associated with classic severe pernicious anemia are not often encountered in modern practice. There are two reasons for this alteration in the character of the disorder. In the first place, patients tend to consult their physicians early, at a time when symptoms may seem inconsequential. The only complaint may be slight weakness or fatigue, or perhaps soreness of the tongue. There may be no detectable pallor at this time, and even if the hemoglobin concentration is determined, anemia may be so mild in degree as to arouse little concern. The diagnosis at this stage is often overlooked. Second, patients with the early symptoms of pernicious anemia are very likely to receive therapeutic preparations which in varying degree are effective in overcoming the manifestations of the disease before the diagnosis has been established. The very nature of the initial symptoms makes it likely that a multivitamin or hematinic preparation will be prescribed, or even procured by the patient without medical advice. Most proprietary vitamin preparations contain folic acid, often in addition to vitamin B_{12}, intrinsic factor and a host of other substances. Administration of these preparations is followed by gratifying clinical improvement. Symptoms subside and anemia disappears. However, the need for adequate therapy for the duration of life is not recognized. Sooner or later relapse occurs, and often neurologic manifestations appear.[1]

In the past five years, 14 of the new cases of pernicious anemia seen at the Johns Hopkins Hospital have presented with crippling neurologic disease in the absence of an appreciable degree of anemia. In some of these the blood and bone marrow were entirely normal. All of these patients were seriously disabled; several were unable to stand or to control the bladder (figure 1). All have residual neurologic manifestations after prolonged and intensive parenteral therapy with vitamin B_{12}. In most cases it was definitely established that the patient had been taking a vitamin preparation containing folic acid.

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From the Department of Medicine, the Johns Hopkins University and Hospital.

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The possibility of pernicious anemia should be considered in any adult patient with an unaccountably subnormal hemoglobin value. Careful examination of the blood will show macrocytosis if anemia is present. However, it is important to remember that red cell abnormalities are slight, and the marrow pattern may not be diagnostic when anemia is mild. If there is a favorable response to treatment with parenterally administered vitamin B_{12}, the diagnosis is reasonably well established. A history of anemia which responded to treatment with a vitamin or hematinic preparation suggests the possibility of pernicious anemia. Appropriate tests should be performed to exclude this disease in any patient who complains of soreness of the

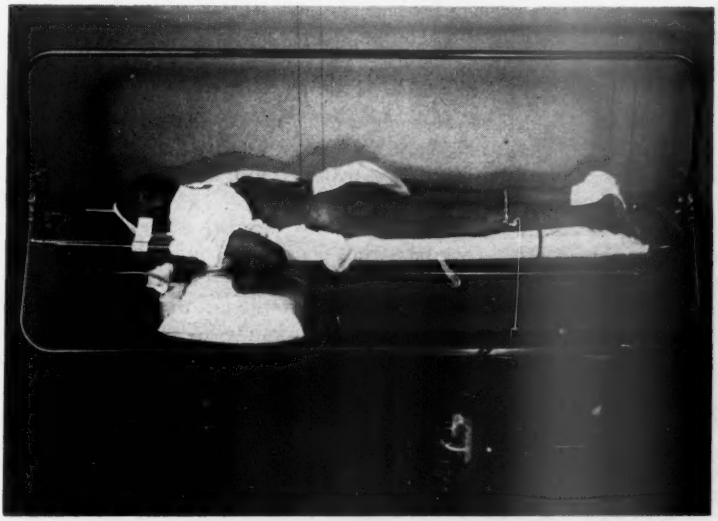

FIG. 1. This 66 year old woman for months had been taking a proprietary multivitamin preparation which contained folic acid. She had never previously had symptoms of pernicious anemia, but while receiving multivitamins rapidly developed extremely severe subacute combined degeneration. She was found to have achlorhydria, and the alimentary absorption of radioactive vitamin B_{12} was markedly impaired. After months of intensive parenteral therapy with vitamin B_{12} she has regained some control of bladder function, but it seems apparent that she will remain a helpless invalid because of permanent damage to the nervous system. A few millionths of a gram of vitamin B_{12}, administered parenterally, could have prevented this incapacitating disorder.

tongue. Neurologic manifestations of subacute combined degeneration should always be considered as probably due to pernicious anemia, even though there are no hematologic abnormalities.

DIAGNOSIS OF PERNICIOUS ANEMIA

An extremely difficult problem is presented by the case in which the diagnosis of pernicious anemia was never definitely proved but in which

therapy has been adequate to induce or maintain a remission. The blood and marrow are normal, and the demonstration of gastric achlorhydria makes the diagnosis acceptable but by no means establishes it. If therapy is withheld, relapse may not occur for several years, so that this is an unsatisfactory diagnostic test. A very helpful solution to this problem has become available with the use of tracer tests employing vitamin B_{12} labeled with radioactive cobalt.[2-8] A small amount of the tagged vitamin is given orally and the fraction which is absorbed from the intestinal tract is measured. In pernicious anemia, absorption is impaired because of the deficiency of intrinsic factor.

Since 1951 we have used radioactive vitamin B_{12} in studies of more than 100 individuals. When an appropriate oral dose is administered, the presence of an absorption defect is readily demonstrated. Impaired absorption is regularly found in pernicious anemia and may also be encountered following total gastrectomy, in sprue and in association with lesions of the small intestine. Impaired absorption was not demonstrated in normal subjects of older age groups or in patients with a variety of diseases unrelated to pernicious anemia. Achlorhydria per se was not associated with reduced vitamin B_{12} uptake. In most of our studies the amount of radioactive material absorbed was determined by measuring the residual radioactivity of the stools. This is a time-consuming and laborious process, requiring total stool collections for not less than six days. The method has the advantage of permitting very accurate measurement. Schilling[9] devised an ingenious technic in which the radioactive material absorbed from the intestine is flushed out into the urine by means of a parenteral injection of a large amount of inert vitamin B_{12}. Radioactive measurements are then made on the urine rather than on the feces. This procedure is less precise, since all of the radioactive vitamin absorbed may not be excreted in the urine. It has the great advantage of simplicity, however, and the test is completed in only 24 hours. The Schilling test has been widely used, with extremely satisfactory results. We have found it to be a reliable clinical test of inestimable value in the diagnosis of pernicious anemia in patients who are in remission as a result of previous therapy. The procedure can easily be carried out in any laboratory in which there are facilities for radioactive measurements.

Treatment of Pernicious Anemia

When refined liver extract became available, completely satisfactory treatment for pernicious anemia was at hand. Patients adequately treated with parenteral liver preparations remained in complete remission throughout their lives. No form of treatment can accomplish more, and a number of therapeutic regimens frequently employed in recent years have accomplished much less. In particular, the use of folic acid in the past decade has in many instances permitted neurologic manifestations to develop while the blood remained normal.

The therapeutic effect of liver extract is attributable to the vitamin B_{12} which it contains. The results of treatment of pernicious anemia with vitamin B_{12} are no better than those obtained with liver extract. Some authors [10, 11] have reported that vitamin B_{12} does not provide complete replacement therapy in pernicious anemia, but the experience of other investigators does not support this contention.[12] More than 50 patients with pernicious anemia in the Hematology Clinic of the Johns Hopkins Hospital have had no therapy other than vitamin B_{12} in the past six years and all remain in complete remission. We have not encountered the hypoprothrombinemia * and macrocytosis which have been described by others during treatment with vitamin B_{12}.

Current interest in the treatment of pernicious anemia centers about the use of orally administered preparations. When vitamin B_{12} is combined with intrinsic factor, absorption of the vitamin is facilitated. Steady progress is being made in the purification of intrinsic factor, and preparations of considerable potency are now available. Several commercial preparations contain a mixture of vitamin B_{12} and a source of intrinsic factor for oral treatment of pernicious anemia. Preliminary observations indicate that

TABLE 1

Patients with Pernicious Anemia Treated with Orally Administered Vitamin B_{12}

Remission induced by oral therapy	17
Remission induced and subsequently maintained by oral therapy	14
Remission maintained by oral therapy	14
Total	45

these are satisfactory, although careful observation of a large group of patients over a long period of time will be required to establish that these preparations are as reliable as is the parenteral injection of vitamin B_{12}. It can be said with certainty that the amount of vitamin B_{12} which can be absorbed from the gastrointestinal tract under the most favorable conditions is far less than that which is customarily injected parenterally. Therefore, when intensive therapy is indicated, as in the patient with neurologic manifestations, parenteral therapy should always be used.

When very large amounts of crystalline vitamin B_{12} are given orally in the absence of intrinsic factor, satisfactory therapeutic responses may be obtained. The doses required for these effects are measured in milligrams rather than in micrograms.[13, 14, 15] In 1950 we initiated an experimental study to determine whether orally administered vitamin B_{12} alone is adequate treatment for pernicious anemia.[12] Forty-five patients have now been treated in this way † (table 1). Thirty-one were in hematologic

* Plasma prothrombin measured by the two-stage technic in 15 of our patients maintained for years on vitamin B_{12} alone was well within the normal range. The lowest values obtained were higher than values obtained in some normal subjects.

† The vitamin B_{12} used in these studies was generously provided by Merck and Co., Inc., Rahway, New Jersey.

relapse when first treated. Most of these patients were hospitalized and placed on a diet deficient in vitamin B_{12}. After completion of the initial studies, a single oral dose of vitamin B_{12}, ranging from 3,000 to 10,000 μg, was given in the morning with the patient fasting. After this single dose, additional therapy was withheld until it was clear that no further improvement was taking place. A number of patients were observed for more than a month before additional treatment was given. The clinical and hematologic responses to these large oral doses were in most instances entirely comparable to those seen after parenteral injection of 30 or more micrograms of the vitamin (figure 2). Soreness of the tongue and gastro-

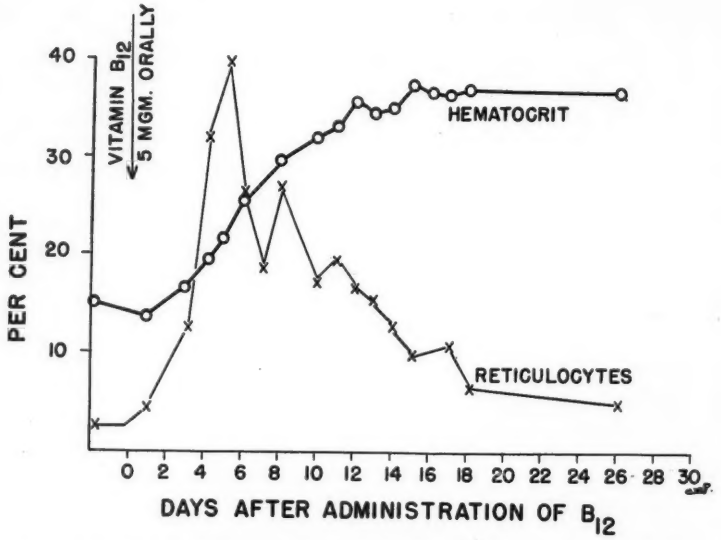

FIG. 2. Hematologic response of a patient with pernicious anemia to a single oral dose of 5,000 μg of vitamin B_{12}.

intestinal symptoms subsided. In several cases neurologic manifestations improved. Several patients developed a complete hematologic remission after a single oral dose. Three patients responded suboptimally to oral therapy. Parenteral injection of the vitamin in each of these three cases failed to accelerate the hematologic improvement. In two the retarded response was associated with infection. The third patient was subsequently allowed to go into relapse and on a second trial responded well to orally administered vitamin B_{12}. In addition to the cases of classic pernicious anemia, one patient with megaloblastic anemia following total gastrectomy and one with a pernicious anemia-like syndrome associated with multiple

TABLE 2

Patients Initially Treated and Maintained in Remission with Orally Administered Vitamin B_{12}*

Patient	Months	Hematocrit	
		Initial	Present
C. J. 55 CF	56	14.0	51.0
E. T. 44 WF	39	13.7	42.0
B. C. 61 CF	36	16.9	44.4
W. M. 84 WM	31	22.0	45.8
T. L. 54 WM	27	26.0	45.1
E. W. 68 CF	27	24.0	43.0

* These patients were brought out of relapse by oral therapy. The initial dose ranged between 3,000 and 10,000 μg of vitamin B_{12}. The maintenance dose in each case was 1,000 μg given as a single tablet once a week.

diverticula of the jejunum also responded well to single oral doses of the vitamin.

Information currently at hand makes it seem probable that extremely high concentrations of vitamin B_{12} in the intestine are required if adequate amounts are to be absorbed regularly in the absence of intrinsic factor. A single dose of less than 1,000 μg appears to be suboptimal, and some patients have failed to respond to daily doses of as much as 250 μg.[16, 17, 18] In attempting oral maintenance therapy, therefore, we decided to use a single large dose once a week, rather than smaller doses at daily intervals.

Of the 31 patients brought into remission by orally administered vitamin B_{12}, 14 have continued on oral therapy for periods ranging for from four months to almost five years. All 14 remain in complete remission, and eight have now been under continuous maintenance therapy for more than two years (table 2). The maintenance dose has been 1,000 μg of vitamin B_{12}, given as a single tablet once a week.

TABLE 3

Patients Maintained in Remission for More Than Three Years by Orally Administered Vitamin B_{12}*

(1,000 micrograms once per week)

Patient	Months	Hematocrit	
		Initial	Present
M. D. 63 WF	39	43.8	45.0
B. S. 73 CF	39	45.0	43.4
R. F. 49 WF	39	44.8	43.7
T. S. 50 WF	39	41.9	40.7
V. F. 48 CF	39	41.5	40.3
A. M. 56 WF	38	44.8	42.2
M. S. 67 WF	38	46.2	47.2
M. G. 70 CF	36	41.9	42.7

* These patients, previously maintained on parenteral therapy, were in remission at the onset of oral therapy. All have remained in complete remission.

Fourteen additional patients had previously been maintained on parenteral therapy and were in remission at the time oral therapy was instituted. These patients have been receiving 1,000 μg of vitamin B_{12} orally once a week for 15 months or longer, and all remain in remission. Hematocrit values before and after oral maintenance therapy in those of this group treated for more than three years are shown in table 3.

The results of this and of comparable studies [19] indicate that patients with pernicious anemia can be satisfactorily treated by the oral administration of large amounts of vitamin B_{12} in the absence of intrinsic factor or other adjuvants. Therapeutic effects appear to be as good as those obtained with oral preparations containing concentrates of intrinsic factor. The

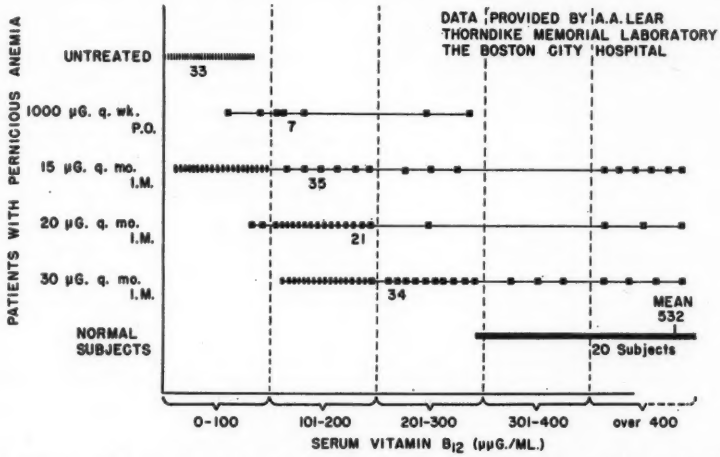

FIG. 3. The concentrations of vitamin B_{12} in the serum of seven patients maintained for prolonged periods on 1,000 μg of vitamin B_{12} orally once a week are compared with those of normal subjects and of patients with untreated and parenterally treated pernicious anemia. Blood for these determinations was drawn just prior to administration of a regularly scheduled dose. All of the treated patients were in clinical remission.

advantage of crystalline material is that it can be assayed by weight, whereas the potency of intrinsic factor preparations must necessarily be measured in terms of the response produced when administered to patients with pernicious anemia.

While these studies were in progress, Lear and his associates [20] were determining the serum vitamin B_{12} concentrations of a large group of patients at the Boston City Hospital. We were fortunate to have their collaboration in measuring the vitamin B_{12} levels in the serum of seven of our patients who had been maintained for prolonged periods of time on 1,000 μg of B_{12} orally once a week. The results can be compared directly with those obtained in other patients on various parenteral dosage schedules

(figure 3). It is clear that the amount of vitamin B_{12} absorbed from the intestine, even with these large doses, is not sufficient to restore the serum concentration to normal. Two patients had extremely low serum levels even though they appeared to be in complete clinical and hematologic remission. These data suggest that the oral dosage schedule employed, 1000 μg once a week, is suboptimal, and that larger amounts would be required to restore tissue saturation. Evidence has been provided by others [14, 19, 21] that the concentration of vitamin B_{12} in the serum of patients with pernicious anemia can be restored to normal levels if adequate oral doses are given.

It is important to emphasize that relatively little vitamin B_{12} can be absorbed from any orally administered preparation in contrast to the large amount which can be injected parenterally. Furthermore, the ability of various patients to absorb the vitamin differs. The complete effectiveness of parenteral therapy, which requires injections no more often than once a month, has been well established. At the present time it would seem wise for most patients with pernicious anemia to continue to receive parenteral therapy. However, if oral therapy is to be used, crystalline vitamin B_{12} alone in milligram doses appears to be as effective as smaller amounts of the vitamin combined with intrinsic factor.

SUMMARIO IN INTERLINGUA

Patientes monstrante le precoce manifestationes de anemia perniciose es frequentemente tractate con preparatos multivitaminic o hematinic que contine acido folic, mesmo ante le diagnose es definitemente establite. Per consequente, le curso clinic del morbo es alterate, e manifestationes neurologic pote resultar in le absentia de anemia. Le diagnose es frequentemente difficile a establir in patientes tractate in iste maniera. Le uso de tests a etiquettage con un forma radioactive de vitamina B_{12} es de specific valor diagnostic in tal casos.

Therapia parenteral con vitamina B_{12} remane le tractamento de selection, sed certe preparatos que es administrate per via oral pare therapeuticamente efficace.

In le presente studio 45 patientes con anemia perniciose esseva tractate con vitamina B_{12} in forma crystallin, administrate oralmente sin factor intrinsec. Quando 3 a 10 milles μg de vitamina B_{12} esseva administrate per via oral e in un sol dose a patientes in stato de recidiva, le responsas clinic e hematologic esseva simile al responsas resultante del therapia parenteral. Il esseva possibile mantener le patientes in stato de remission complete per le administration de un sol tabletta con 1000 μg B_{12} un vice per septimana. Per iste regime 11 patientes ha essite mantenite de maniera satisfactori durante periodos de plus que tres annos. Totevia, recente mesurationes del concentration seral de vitamina B_{12} in 7 de iste patientes indica que le nivellos seral que resulta de iste dosage es probabilemente suboptimal e que plus grande quantitates es requirite pro restaurar le saturation del texitos.

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CRYPTOCOCCOSIS: CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS *

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CRYPTOCOCCOSIS (torulosis) is an infection which occurs more frequently than is generally appreciated. Clinically the early diagnosis of this disease is difficult. However, if the possibility of cryptococcosis is considered in the differential diagnosis of any chronic infection or of any disease of obscure origin, the diagnosis might be made more frequently.

Cryptococcosis is caused by a yeastlike fungus, *Cryptococcus neoformans* (*Torula histolytica*). Infections caused by this organism usually terminate in fatal meningo-encephalitis. However, the fact that lesions elsewhere in the body often precede the lesions in the central nervous system is sometimes overlooked. Often signs and symptoms produced by these lesions in tissues outside the central nervous system occur early in the course of the infection, and occasionally they predominate throughout the course of the disease.

Since 1947, six patients with cryptococcosis have been seen at the Mayo Clinic. Three cases seen at this institution prior to 1947 have been reported previously by Tinney and Schmidt.[1] A review of all nine cases makes apparent certain of the clinical features encountered in this type of infection. We also have had the opportunity of observing two other patients with probable disseminated cryptococcosis, but we were not able to obtain conclusive bacteriologic data. These latter two patients are not included in this report.

CASE REPORTS

Case 1. A white housewife from Iowa, 61 years of age, was first seen at the Mayo Clinic on February 1, 1949, because of cervical adenopathy and fever. She had first noticed the cervical adenopathy in the summer of 1948. Following this, she had noticed anorexia, chilliness, night sweats and mild epigastric distress. She had gradually lost 15 pounds (6.8 Kg.). Two abscessed teeth had been extracted, without relief of symptoms. A cervical node had been excised and a diagnosis of Hodgkin's disease had been made from the microscopic appearance of the node.

Physical examination at the time of the woman's admission to a Rochester hospital in February, 1949, revealed lymphadenopathy involving the anterior and posterior cervical nodes, the supraclavicular nodes and the axillary nodes. A faint systolic murmur was heard over the entire precordium. The spleen was palpable two fingerbreadths below the margin of the ribs. Blood pressures were 144 mm. of mercury systolic and 78 mm. diastolic. Physical examination otherwise gave essentially negative results.

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From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation in Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Positive results of laboratory examination were as follows: The concentration of hemoglobin in the blood was 11.1 gm. per 100 c.c. Erythrocytes numbered 3,840,000 and leukocytes 5,200 per cubic millimeter of blood. The differential leukocyte count was 18% lymphocytes, 5% monocytes, 42% neutrophils, 32% eosinophils and 3% basophils. Marked eosinophilia was evident in a special blood

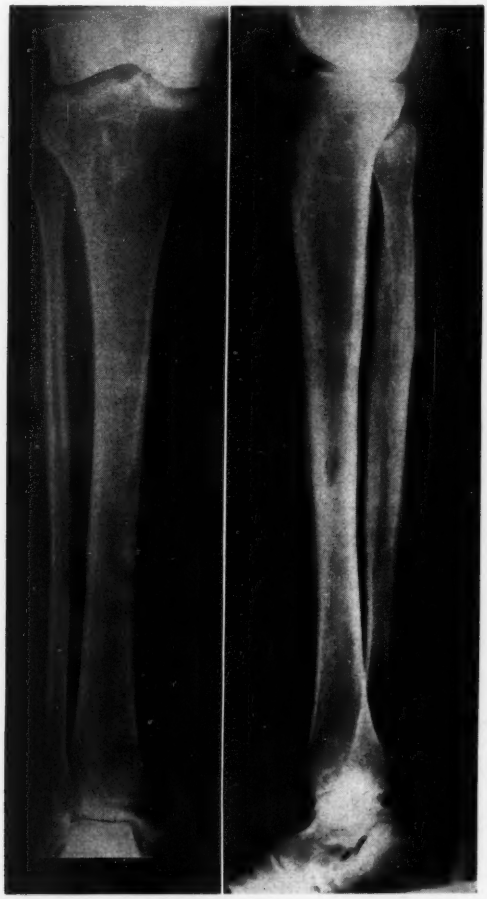

FIG. 1. Osteomyelitis of the tibia attributable to *Cryptococcus neoformans*.

smear, but otherwise the smear was negative. Laboratory examinations which gave normal results were the sedimentation rate, serum albumin, serum globulin, urinalysis, agglutination tests for brucellosis and tularemia, roentgenograms of the thorax and of the left hand, and an electrocardiogram.

On March 22, 1949, a very firm node was excised from the left cervical region.

The surgeon reported that grossly this node felt like those involved with Hodgkin's disease. The original pathologic report was of Hodgkin's disease (granulomatous type). Later, however, the node was reëxamined and was reported to be composed merely of necrotic inflammatory tissue. After culture of the node and inoculation of the material into guinea pigs, bacteria or fungi failed to grow. The patient was given a course of roentgen therapy applied to the cervical nodes and they regressed satisfactorily.

The patient felt well in the fall of 1949, but in early 1950 she noticed recurrence of weakness and fatigue. In May, 1950, definite tenderness and some swelling developed below the right eye. Physical examination in May, 1950, revealed enlarged lymph nodes in the posterior cervical, right supraclavicular, right axillary and inguinal regions. Results of laboratory examinations at this time were as follows:

FIG. 2. Cellulitis of the right malar region attributable to *Cryptococcus neoformans*.

On urinalysis a few erythrocytes were found, but otherwise results were negative. The concentration of hemoglobin in the blood was 10.3 gm. per 100 c.c. Leukocytes numbered 5,400 per cubic millimeter of blood, 32% of which were lymphocytes; 2%, monocytes; 61%, neutrophils; 5%, eosinophils. The sedimentation rate of erythrocytes was 51 mm. per hour by the Westergren method. The enlarged nodes were subjected to further roentgen therapy.

The swelling in the right malar region gradually increased, and swelling was noted also in the lower part of the right leg and in the dorsum of the right foot. The patient continued to feel weak, and a slight cough developed.

On July 18, 1950, a fluctuant mass was found under the right eye. Other fluctuant masses were found over the anterior surface of the right tibia and on the dorsum of the right foot. Localized tenderness was noticed in the median frontal

region of the skull. Laboratory studies gave the following results: A few erythrocytes were found in the urine, which was otherwise negative to examination. The concentration of hemoglobin was 10.6 gm. per 100 c.c. of blood. Erythrocytes numbered 3,730,000 and leukocytes, 5,000 per cubic millimeter of blood. Of the leukocytes, 28% were lymphocytes; 17%, monocytes; 54%, neutrophils; 1%, eosinophils. The sedimentation rate was 123 mm. per hour. Roentgenograms of the right leg (figure 1) gave evidence of two regions of destruction in the right tibia; one, just below the tibial tubercle, had eroded through the cortex, and the other was at the junction of the middle and lower thirds of the tibia. There was also a destructive lesion in the right third metatarsal. Cultures of the urine and of the blood, including special studies for fungi, were reported as negative. Roentgenograms of the thorax again did not reveal anything abnormal.

The lesion in the right malar region (figure 2) was aspirated and a pure culture of *Cryptococcus neoformans* was obtained. Incision made over the fluctuant area

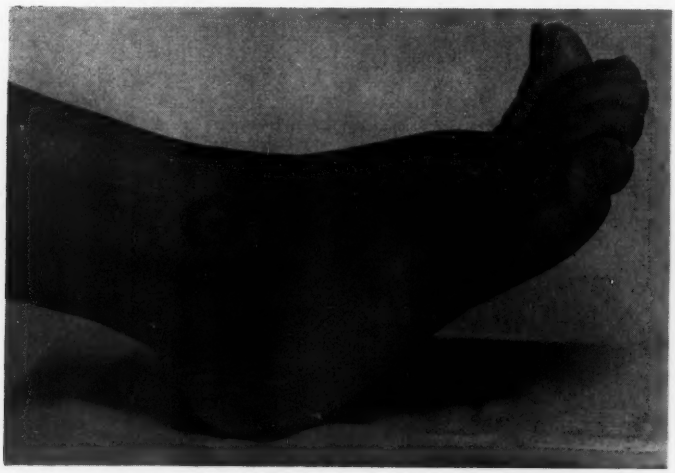

FIG. 3. Osteomyelitis of the right third metatarsal with overlying abscess. A pure culture of *Cryptococcus neoformans* was obtained from this lesion.

at the point of the right tibial tubercle yielded a milky, mucoid fluid containing a few flecks of old blood. The cavity was subjected to curettage and the wound was closed. Microscopic examination of the tissue from the right tibia gave evidence of granulomatous inflammation; also, yeastlike, budding organisms surrounded by wide zones of mucoid, capsular material were found. The evidence of cellular reaction in the tissues consisted mainly of the presence of macrophages and fairly numerous giant cells. Culture of the material obtained from the abscess in the right tibia revealed *Cryptococcus neoformans*. *Cryptococcus neoformans* was obtained on culture of material aspirated from the abscess (figure 3) of the right foot.

A further course of roentgen therapy was given over the fluctuant masses and they were gradually reabsorbed. However, after a few months headache and unsteadiness of gait developed. It became impossible for the woman to walk without help. In the early part of 1951 she became comatose, and she died at home soon afterwards. Postmortem examination was not made.

Case 2. A white male physician who had lived in North Dakota for many years was registered at the clinic on March 3, 1950. He was 72 years of age. He had felt well until February 14, 1950, at which time malaise and retro-orbital headache had developed. Three days later he had started to vomit, and he had vomited frequently thereafter. The headache had persisted and had increased in severity.

At the time of the patient's admission to the hospital his neck was moderately stiff. He was deaf in the left ear. The ocular fundi were normal. There were moist râles in the bases of both lungs; however, consolidation could not be detected. Physical examination otherwise gave negative results.

Significant results of laboratory examinations were as follows: Leukocytes numbered 9,000 per cubic millimeter of blood, 14% of which were lymphocytes; 3%,

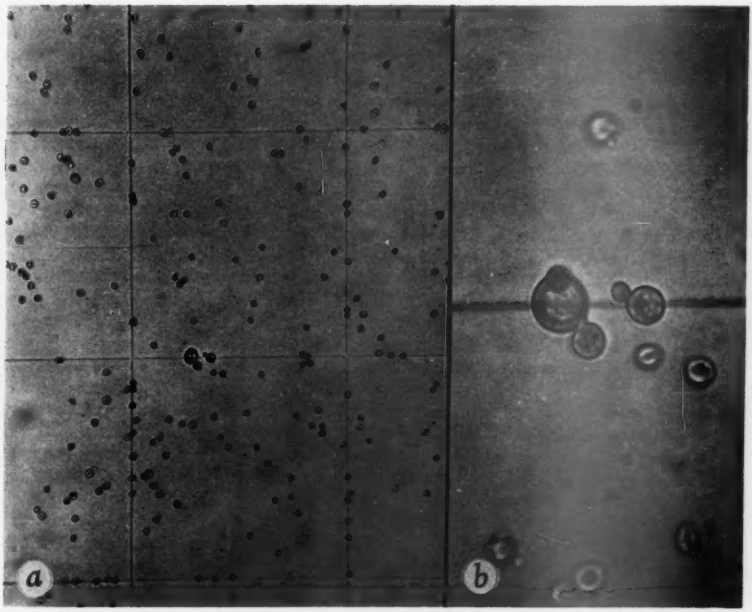

FIG. 4. *Cryptococcus neoformans* as seen, unstained, in an improved Neubauer counting chamber with Fuchs-Rosenthal ruling. *a*, × 150; *b*, × 660.

monocytes; 81%, neutrophils; 2%, eosinophils. The spinal fluid contained 84 lymphocytes and 17 polymorphonuclear cells per cubic millimeter, as well as many cryptococci (figures 4*a* and *b*). There were 90 mg. of protein, 21 mg. of sugar and 585 mg. of chloride per 100 c.c. of spinal fluid. The Wassermann reaction of the spinal fluid was negative and the gold curve was normal. Culture of the spinal fluid revealed *Cryptococcus neoformans*. A roentgenogram of the thorax gave evidence of pneumonia in the base of the left lung and of thickening of the apical pleurae. An electro-encephalogram revealed grade 3 delta rhythm bilaterally in the frontal areas and spreading to the temporal regions bilaterally.

The following laboratory studies gave normal results: urinalysis, determination of the concentration of hemoglobin, erythrocyte count, sedimentation rate, concen-

tration of blood urea, plasma carbon dioxide, serum bilirubin and Kahn flocculation test of the blood. A roentgenogram of the skull was negative.

This patient died in his home city a few weeks later.

Postmortem examination was performed by Dr. J. E. LeMar, of Fargo, North Dakota, who kindly sent us his report and consented to its inclusion here. Cryptococcal infection of the central nervous system was widespread. There were numerous cystic lesions in the brain stem and along the basal ganglia. Marked inflammatory changes and thickening of the leptomeninges were noted, as was adhesive arachnoiditis. Numerous pulmonary abscesses were present, but microscopically cryptococci could not be demonstrated in them.

Case 3. A white truck driver from Missouri, 33 years of age, gave a history of having been rejected for Army service in 1943 because of quiescent pulmonary tuberculosis. He had had a nonproductive cough for several years but never had had hemoptysis. In 1946 several teeth had been extracted. In the spring of 1947 he had noticed that he became fatigued easily. His left testis had been painful for a few days at about the same time. In July he had noticed headache and slight vertigo. The headaches had become progressively more severe. On August 15 he had become nauseated and had vomited and, on August 19, he had become irrational. On August 20 he had been admitted to a hospital with a low grade fever. A presumptive diagnosis of tuberculous meningitis had been made, and he had been given streptomycin intramuscularly and intrathecally.

On September 18, 1947, the patient was admitted to a hospital in Rochester, Minnesota. He was disoriented and confused, and his neck was markedly rigid. Kernig's and Lasègue's signs were elicited. Ophthalmoscopic examination revealed both optic discs to be elevated 1 diopter. Hemorrhages or exudates could not be seen in the fundi but there was evidence of old traumatic choroiditis. Blood pressures were 120 mm. of mercury systolic and 60 mm. diastolic. Nothing else of note was found on physical examination.

Significant laboratory examinations, made from September 18 to October 1, inclusive, gave the following results: Leukocytes numbered 7,000 per cubic millimeter of blood, 94% of which were neutrophils. The sedimentation rate of erythrocytes (Westergren method) was 78 mm. per hour. Roentgenograms of the thorax gave evidence that a diffuse, nodular, fibrotic, infiltrative process involved the upper two thirds of the right pulmonary field and the lower two thirds of the left. On September 18 values for constituents of the spinal fluid were as follows: total protein, 80 mg. per 100 c.c.; sugar, 22 mg. per 100 c.c.; chlorides, 687 mg. per 100 c.c. Lymphocytes in the spinal fluid numbered 34 and polymorphonuclear cells, 11 per cubic millimeter. The result of the Kolmer flocculation test performed on spinal fluid was doubtful, and a colloidal gold curve was normal. The initial pressure of the spinal fluid was 38 cm. and the final pressure, 10 cm. Culture of the spinal fluid yielded *Cryptococcus neoformans.*

Laboratory studies which gave normal results were urinalysis, concentration of hemoglobin, flocculation test for syphilis performed on the blood, roentgenographic examination of the head, cultures of the blood, bronchial cultures and agglutination test for *Pasteurella tularensis.*

The patient was given 90 grains (6 gm.) of sulfadiazine daily for 6 days. He was dismissed from the hospital on October 1 but the medication was continued at home. The patient's condition steadily deteriorated, however, and he died on October 16, 1947. Postmortem examination was not performed.

Case 4. The patient was a 56 year old white electrician from Iowa who gave a history of having had rheumatic fever and rheumatic heart disease in 1914. He had remained well thereafter until 1948, when a respiratory infection had developed; this had been followed by a chronic cough with purulent sputum. The cough had

persisted but the man had been able to perform his work without difficulty. In 1952 enlarged posterior cervical nodes had been noticed. In September, 1952, one of these nodes had been excised elsewhere and, on examination of it, a diagnosis of noncaseous lymphadenitis, consistent with Boeck's sarcoid, had been made from the specimen. In April, 1953, the patient first had noticed constant frontal headache. He had been able to continue work until the first of June, when he had begun to vomit frequently. Pain had developed in the lower lumbar region at about that time.

At the time of the patient's admission to a hospital in Rochester, on May 22, 1953, he appeared in obvious distress. His body temperature was not elevated. Cervical, axillary and inguinal nodes were enlarged. His neck was slightly stiff. He walked on a wide base but definite muscular stiffness could not be demonstrated. On ophthalmoscopic examination, a grayish, slightly elevated lesion, 1 disc in diameter, was found just temporal to the macula of the right eye.

Results of laboratory examinations were as follows: Leukocytes numbered 10,100 cells per cubic millimeter of blood, of which 7% were lymphocytes, 2% were monocytes and 91% were neutrophils. In roentgenograms of the thorax there was evidence of a small fibrotic lesion at the level of the right fourth anterior intercostal space. The initial spinal fluid pressure was 23 cm. of water. The concentration of protein in the spinal fluid was 90 mg. per 100 c.c.; of sugar, 38 mg. per 100 c.c.; of chlorides, 649 mg. per 100 c.c. Lymphocytes in the spinal fluid numbered 34 per cubic millimeter. The Kolmer flocculation test of the spinal fluid gave a negative result, and the colloidal gold curve was normal. An electro-encephalogram gave evidence of generalized dysrhythmia. *Cryptococcus neoformans* was cultured from the cerebrospinal fluid. The concentration of hemoglobin, the erythrocyte count, the sedimentation rate, the Kline flocculation test for syphilis, roentgenographic examination of the skull and a tuberculin skin test gave results which were negative or within normal limits. Biopsy of a lymph node from the left axilla gave evidence that inflammation and hyalinization had been taking place within it. *Cryptococcus neoformans* was obtained in cultures from this node.

The patient's condition steadily deteriorated. The rectus muscle of the left eye became paralyzed. The man became confused, disoriented and finally comatose. He died on June 5, 1953.

On postmortem examination extensive inflammatory changes were found in the spleen, liver, prostate gland, meninges, kidneys, lungs and adrenal glands. Organisms, apparently cryptococci, could be seen in these organs on microscopic examination. Chronic rheumatic endocarditis was also present. *Cryptococcus neoformans* was cultured from an aortic node and a mediastinal node, and from the cerebrospinal fluid.

Case 5. A white school girl, 16 years of age, who had been living on a farm in Minnesota, had a progressively developing frontal headache, anorexia, a nonproductive cough and weakness. She dated its onset from February 1, 1948. Two weeks later she noticed fever for the first time. Her cough had become productive of a moderate amount of mucopurulent sputum. There had been no hemoptysis.

At the time of her admission to a Rochester hospital on March 9, 1948, lymphadenopathy was present in the postoccipital, cervical, axillary and inguinal regions. The skin was dry and there was a malar flush. In the pharynx, as part of an inflammatory reaction, were ulcerated areas covered with exudate. The upper part of the abdomen was tender to pressure. The joints were not swollen or red, but movement of them was painful. Blood pressures were 104 mm. of mercury systolic and 72 diastolic. Each ocular disc was elevated about 1 diopter. The retinal arterioles were dilated slightly, and the retinal veins were about twice normal size. Several white, cottonwool exudates were clustered around each disc, but hemor-

rhages were not seen. Physical examination otherwise gave essentially negative results.

Laboratory studies were as follows: In the urine were considerable albumin, granular casts and erythrocytes. The specific gravity of the urine was 1.027. Leukocytes numbered 1,500 per cubic millimeter of blood, of which 18% were lymphocytes; 5%, monocytes, and 73%, neutrophils; 4% were unclassified. The rate of sedimentation of erythrocytes (Westergren method) was 55 mm. per hour. In the electrocardiogram were isoelectric T waves in Leads I, II and III; otherwise the tracing was negative. The value for total serum protein was 5 gm. per 100 c.c., of which 2.6 gm. were albumin and 2.4 gm., globulin. In a liver function test, 18% of Bromsulphalein was retained in one hour. In marrow obtained by sternal aspiration there was a shift to the left in the myeloid line, but the examination did not disclose other abnormalities. The concentration of hemoglobin and blood urea, the number of erythrocytes and blood platelets, results of the Kline flocculation test, the value for serum bilirubin and the appearance of roentgenograms of the thorax all were within normal limits. Two cultures of the blood gave negative results, as did agglutination tests for brucellosis, typhoid fever and paratyphoid fever.

The patient's condition continued to deteriorate after her hospitalization. Penicillin, 240,000 units, was given daily without benefit. The girl died on March 16, 1948.

At postmortem examination lymphadenopathy was found, accompanied by a granulomatous reaction. In sections of lymph node, cryptococci were present within giant cells. The lungs were edematous, and most of the pulmonary alveoli were filled with fibrin, erythrocytes and macrophages. Cryptococci could be demonstrated in many portions of the lungs. The spleen was twice normal size, but cryptococci could not be found on microscopic examination. There was focal calcification of the kidneys and evidence of healed pyelonephritis. The brain was not examined. The diagnosis in this case was made only by identification of the organism on direct examination. Cultures were not made.

Case 6. A white male business executive from Minnesota, 54 years of age, had had an episode of vague distress in the lower part of the abdomen in February, 1953. The distress had recurred at varying intervals.

The patient registered at the Mayo Clinic on November 23, 1953. Physical examination gave essentially negative results. Roentgenograms of the gastrointestinal tract furnished evidence of the presence of a duodenal ulcer but of nothing else abnormal. In roentgenograms of the thorax was a poorly defined shadow opposite the second anterior intercostal space on the right. There had been no evidence of this lesion in roentgenograms of the thorax made on March 5, 1952.

Results of acid-fast stains of the sputum and cytologic examination of it for malignant cells were negative. The urine, the concentration of hemoglobin and the number of erythrocytes and of leukocytes in the blood all were normal. The Kline flocculation test gave a negative result.

A roentgenogram of the thorax, made on December 28, 1953, showed that the previously described area of nodular density had increased appreciably in size. On January 5, 1954, thoracotomy was performed. A firm, rounded nodule was found in the posterior part of the periphery of the right upper lobe. The lesion was excised. The removed tissue proved to be a granuloma with giant cells containing encapsulated, yeastlike organisms. Cultures made from the lesion yielded *Cryptococcus neoformans*.

The patient's postoperative course was uneventful. He was given 20 drops of potassium iodide daily for two months. There has been no evidence of dissemination of the infection in the subsequent 18 months.

Comment

The portal of entry of Cryptococcus has not been definitely established, but most investigators believe that it is either the lungs or the skin. In our cases 1 and 3 there was a history of recent extraction of teeth.

Wade and Stevenson [2] have carried out some investigations concerning dissemination of the infection after the organism has gained admission to the body. They introduced *Cryptococcus neoformans* into white mice intravenously, intracerebrally, intraperitoneally, intrathecally and subcutaneously. In no instance did involvement of the central nervous system develop in the absence of systemic involvement. The lesions were of most frequent occurrence and were most extensive in the lungs of the mice, but extensive lesions were also present in the brain and kidneys. The liver and spleen were involved less frequently, and the lesions therein were smaller.

The initial signs and symptoms of cryptococcosis are often produced by lesions in the lungs, lymph nodes or bones. Occasionally, however, signs or symptoms do not appear until the central nervous system has become involved. Of the nine cases of cryptococcosis which have been seen at the Mayo Clinic in recent years (including the three reported by Tinney and Schmidt [1]), an initial symptom in four was related to the respiratory tract; in all of these four cases there was a chronic cough. Generalized adenopathy developed later in two of these four cases. In two of the nine cases cervical adenopathy, perhaps due to Hodgkin's disease, was the first abnormality noticed. In one of these two cases osteomyelitis attributable to cryptococci developed later and, in the other, pulmonary symptoms due to cryptococcosis developed before the central nervous system became involved. In three cases of the nine, the initial signs and symptoms were referable to the central nervous system. In two of these three cases the respiratory tract was involved also at the time of our examinations.

Cryptococcosis may remain localized for months or years. However, once the Cryptococcus has gained access to the body it may spread through the lymphatics or blood stream to various tissues or organs.

The reticuloendothelial system is probably always involved at some time in the disseminated form of cryptococcosis. At postmortem examination the liver and spleen are often found to contain lesions. Enlarged lymph nodes have been mentioned in nearly 20% of reported cases. However, only occasionally have cryptococci been isolated from these nodes.[3, 4]

Many investigators have noted the high incidence of association of cryptococcal infections with Hodgkin's disease and similar malignant conditions.[5–7] Zimmerman and Rappaport studied 60 cases of cryptococcosis and found that malignant diseases of the reticuloendothelial system were the most frequently associated conditions, being present in 18 of the 60 cases.[7] Hodgkin's disease accounted for 11, reticulum cell sarcoma for two, leukemia for four, and multiple myeloma for one of these 18 cases. The evidence reported by Zimmerman and Rappaport suggests that patients with

malignant lymphoma and leukemia have an increased susceptibility to cryptococcosis. Lack of resistance to infection in these patients seems to be a part of their primary disease.

Lymphadenopathy was present in three of the cases we are reporting and in one of those previously reported by Tinney and Schmidt.[1] In three of these four cases in which adenopathy was present, a node was excised for examination. Microscopically, the appearance of the tissue in two of these cases in which a node was excised suggested lymphosarcoma of the Hodgkin type. In these two cases, the cryptococcosis may have been

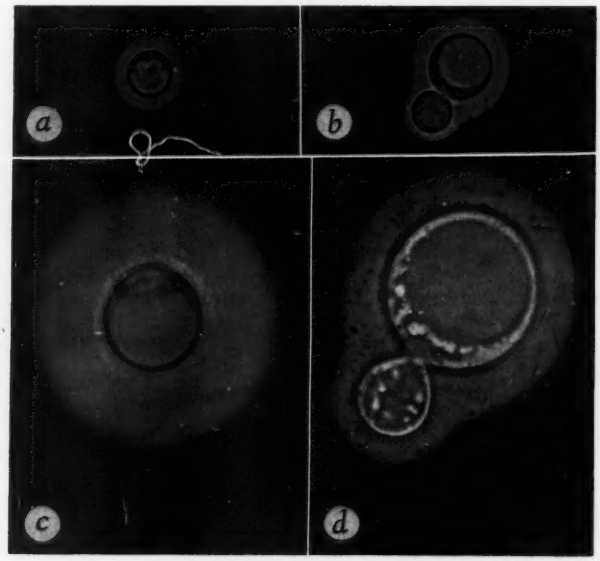

FIG. 5. *Cryptococcus neoformans.* India ink preparations of spinal fluid; *a* and *b*, × 645; *c* and *d*, × 1455.

merely an associated or secondary disease. However, reëxamination of the tissue in one of the two cases failed to reveal changes typical of Hodgkin's disease. The diagnosis of Hodgkin's disease in the other of the two cases was confirmed by reëxamination of the tissue removed at biopsy. In the third case the microscopic appearance of the node was that of a non-caseating granuloma suggestive of sarcoidosis.

The importance of making cultures of lymph nodes removed for examination is apparent. Moreover, a culture for cryptococci should be made of the spinal fluid of any patient with Hodgkin's disease who has meningeal symptoms.

Cryptococcosis should be considered in the differential diagnosis of any

inflammatory condition of the central nervous system.[8-10] The meningo-encephalitis produced by this organism presents a clinical picture indistinguishable from other types of meningo-encephalitis. The condition has been confused clinically with brain tumor and subdural hematoma.

Occasionally the cryptococci can be seen when unstained spinal fluid is examined under a microscope (figure 4), and the similarity of the appearance of cryptococci and normal blood cells has caused confusion in certain instances. India ink preparations of the spinal fluid may reveal the cryptococci and the thick-walled budding cells (figure 5).

Involvement of the meninges by the infection was established at postmortem examination in four of the nine cases studied at this clinic. These patients usually complain of headache, occasionally accompanied by vomiting. Stiffness of the neck is frequently found. Vertigo and visual disturbances are not uncommon.

In our three cases of cryptococcic meningitis, and in the two previously reported by Tinney and Schmidt,[1] the changes in the cerebrospinal fluid were as follows: The number of cells in the cerebrospinal fluid ranged between 34 and 118 per cubic millimeter in the various cases. Lymphocytes always predominated. The amount of protein in the cerebrospinal fluid in each instance was 80 mg. or more per 100 c.c. of cerebrospinal fluid, and the amount of sugar was less than 40 mg. Values for chloride ranged between 585 and 687 mg. per 100 c.c. of spinal fluid.

In systemic cryptococcosis the lung is often found to be involved. Variable physical and roentgenographic findings may be present.[11-15] At times the lesions in the lungs may be so small that they cannot be demonstrated roentgenographically and can be found only at postmortem examination. In most of our cases roentgenograms of the thorax revealed evidence of an inflammatory process in the pulmonary parenchyma. In one case, culture of a solitary granuloma surgically removed from a lung revealed cryptococci. Postmortem examination in three of our cases revealed inflammatory lesions in the lungs, and cryptococci could be demonstrated in these lesions in two of the cases.

In addition to the lesions of the lung, as a result of dissemination of the infection, lesions in almost any organ can be produced and may cause symptoms. Involvement of bone has been noted in about 8% of reported cases of cryptococcosis.[16, 17] The osseous lesions are usually widely disseminated and do not produce much inflammatory response in bone or periosteum. In case 1 it was from osseous lesions in the foot, leg and skull that cryptococci were cultured. Lesions of the skin occur occasionally as part of a disseminated infection. In 13 reported cases,[18] acneform lesions, papular lesions, abscesses or ulcers were the commonest types of cutaneous manifestations. At postmortem examination the kidneys are often found to be involved, although clinical evidence of nephritis has not been reported frequently. In two of our cases evidence of renal involvement was found

at postmortem examination. The adrenal glands may be involved by this infection and adrenal insufficiency from massive destruction of the glands has been reported.[19] In one of our cases involvement of the adrenals was evident at the time of postmortem examination. However, clinical evidence of adrenal insufficiency had not been noted.

Diagnosis of cryptococcosis depends on identification of the organism by culture of pus, sputum, tissue, spinal fluid or other body fluid. Pathogenicity of the organism is usually determined by its effect when injected into mice. One or more negative cultures do not exclude the possibility of cryptococcosis. At times a presumptive diagnosis of cryptococcosis can be made from identification of the organism by direct examination.

The prognosis relative to this disease is poor. The infection may be fulminating or chronic. Remissions are of common occurrence, and patients may remain well for years;[20] eventually most of them succumb to meningo-encephalitis. One case in which cryptococcic meningitis was of nearly 16 years' duration has been reported.[21] The tendency toward remission makes evaluation of therapeutic measures difficult. All of our patients, except the one most recently seen, are dead.

To date there is no satisfactory treatment for disseminated cryptococcosis. Roentgen therapy, sulfonamides, penicillin, streptomycin and iodides have been tried in our cases, without demonstrable effect. One favorable report[22] concerning a patient who received cyclohexidine (Acti-dione) has appeared, but this antibiotic has not been effective in other cases.[23] From observations in the laboratory, Carton and Liebig[24] have suggested trial of combined therapy in which cyclohexidine (Acti-dione) and polymyxin B sulfate are used. We have not seen reports of clinical use of this combination of drugs. We have attempted to evaluate use of sulfonamides in combination with hyperthermia in treatment of animals experimentally infected with cryptococci, but we are not impressed with the applicability of this regimen.

Surgical excision of a localized lesion may eradicate the infection. The one patient in our group who had a localized lesion has remained well since surgical operation but has been followed for only 18 months.

Summary

In nine cases of cryptococcosis, six of which are reported in detail, lungs, bones and lymph nodes were common sites of infection. Most of the patients died of meningo-encephalitis. However, symptoms referable to the lesions elsewhere in the body often preceded the symptoms caused by the lesions of the central nervous system. Chronic cough was an initial symptom in several of the cases, and in these, roentgenograms of the thorax revealed evidence of an inflammatory process in the pulmonary parenchyma. In two of the nine cases there was a history of recent extraction of teeth. The cryptococcal infection was associated with Hodgkin's disease in one

case and possibly in a second one. The meningo-encephalitis produced by the organism presented a variable clinical picture. To date there does not appear to be any satisfactory treatment for disseminated cryptococcosis. Surgical excision of a localized lesion seemed to eradicate the infection in one of our cases.

SUMMARIO IN INTERLINGUA

In nove casos de cryptococcosis—sex del quales es reportate in detalio—pulmones, ossos, e nodulos lymphatic esseva commun sitos del infection. Le majoritate del patientes moriva de meningo-encephalitis. Tamen, symptomas referibile a lesiones alterubi in le corpore precedeva frequentemente le symptomas causate per lesiones del systema nervose central. Tusse chronic esseva un symptoma initial in plures del casos, e in istos roentgenogrammas del thorace revelava signos de un processo inflammatori in le parenchyma pulmonar. In duo del nove casos il habeva un historia de recente extractiones de dentes. Le infection cryptococcal esseva associate con morbo de Hodgkin in un caso e possibilemente in un secunde. Le meningo-encephalitis producite per le organismo presentava un variabile syndrome clinic. Al tempore presente il non pare haber ulle satisfacente tractamento pro disseminate cryptococcosis. In un del casos le excision de un infection local pareva eradicar le infection.

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CHRONIC MASSIVE PULMONARY ARTERY THROMBOSIS *

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SUDDEN death due to massive pulmonary embolism is a relatively common autopsy finding, and the medical literature is replete with studies of cases in this category. However, chronic thrombosis of the main pulmonary artery or of the right or left main branches is, in contrast, a rare finding and reported cases are limited in number. As one descends the pulmonary arterial tree, thrombosis becomes more common, depending upon the diligence with which prosection is done. Certainly lobular thrombosis is seen more frequently than lobar and, in turn, arteriolar thrombosis is far more common than either.

A total of 11,511 consecutive autopsies from Queens General and Triboro Hospitals † from late 1935 through 1954, inclusive, were reviewed; 580 of these cases were from Triboro Hospital, a tuberculosis institution. Twenty-one cases (0.18%) of massive pulmonary artery thrombosis were found. Only those cases with complete occlusion of the main pulmonary artery or the main right or left primary branches were included in this series. The premortem nature of these thromboses and their chronicity were judged by such characteristics as lines of Zahn, lamination of layers, adhesiveness to the vessel wall and degree of organization. Evaluation of the presence of underlying embolus was attempted by such criteria as orientation of lines of Zahn to the flow of blood, leg vein valve markings, evidence of peripheral emboli in lower extremities or pelvis, and clinical histories consistent with episodes of previous pulmonary embolism.

Twenty-one cases of massive pulmonary artery thrombosis are presented (table 1). Twelve were males and nine were females. Their ages ranged from 15 months to 89 years, with the mean age and median age both 59 years. The right main pulmonary artery alone was involved in the process in nine cases, and the left alone in four cases. Both right and left pulmonary arteries were involved in eight cases.

In a few of these 21 cases we were led to speculate as to how the patients were able to remain alive with so little obvious pulmonary circulation. As noted by Brenner [1] in his comprehensive paper on the pathology of the vessels of the pulmonary circulation in 1935, as much as 75% of the pulmonary artery cross section may be occluded before the systolic blood pressure falls, and 90% before death occurs. As he also notes, the pul-

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† These are the units of the Municipal Queens Hospital Center, Jamaica, New York City. Grateful acknowledgment is made to Dr. Gertrude Silverman, Pathologist of the Queens Hospital Center, for her gracious coöperation in the preparation of this article.

TABLE 1

Case No.	Sex	Age, yrs.	Main Pulm. Art. Involved	Pulmonary Disease	Associated Main Path. Diagnosis	Heart	Other Thrombo-emb. Phenomena	Outstanding Symptoms	Additional Features
1	M	26	Right and left	Bilateral far-advanced T.B.	Pulmonary tuberculosis	Cor pulmonale	Massive infarct, right lung	Marked dyspnea	
2	M	50	Right and left	Pulmonary cystic disease, fibrosis, emphysema and bronchiectasis	Chronic pulmonary disease. Mesenteric thrombosis	Right and left hypertrophy	Mesenteric thrombosis, renal and splenic arterial thrombosis	Dyspnea, cyanosis	Cyanosis, upper part of body, secondary polycythemia, luetic aortitis, pulmonary arteriosclerosis
3	M	70	Main trunk and right	Pulmonary fibrosis, acute pneumonia	Bronchopneumonia	Cor pulmonale	Thrombus, right auricular appendage	Increasing dyspnea	Pulmonary arteriosclerosis
4	F	89	Right and left	Acute pneumonia	Arteriosclerotic heart disease	Left ventricular hypertrophy	None	Drowsiness, dyspnea	
5	F	48	Right	Pulmonary tuberculosis, far-advanced	Pulmonary tuberculosis, congestive heart failure	Cor pulmonale and dilatation of all chambers	Mural thrombosis, right auricular appendage. Thrombosis, left innominate vein	Dyspnea, cyanosis	
6	M	62	Right	Carcinoma, right lung, chronic pulmonary infection	Bronchogenic carcinoma	Right heart dilatation	Ball-valve thrombus, left auricle	Dyspnea, cough, cachexia	
7	M	31	Right	Miliary tuberculosis	Progressive disseminated primary tuberculosis	Left ventricular hypertrophy and right ventricular dilatation	Infarct, right lower lobe	Dyspnea, chest pain	P_2 became louder than A_2; pulmonary arteritis

TABLE 1—*Continued*

Case No.	Sex	Age, yrs.	Main Pulm. Art. Involved	Pulmonary Disease	Associated Main Path. Diagnosis	Heart	Other Thrombo emb. Phenomena	Outstanding Symptoms	Additional Features
8	F	57	Left	Pulmonary fibrosis and emphysema	Chronic lung disease. Congestive failure	Cor pulmonale and left ventricular hypertrophy	Infarct, left lower lobe. Thrombosis, right auricular appendage	Dyspnea, cyanosis	Widely dilated pulmonary artery and loud pulmonic diastolic murmur
9	F	78	Right	Congestion and edema	Adenocarcinoma, fundus uteri	Right heart dilatation. Left ventricular hypertrophy	None	Abdominal pain	Metastases to omentum and peritoneum
10	F	46	Left	Pulmonary tuberculosis, far-advanced	Pulmonary tuberculosis	No abnormality	None	Marked dyspnea	
11	F	82	Right	Lung abscess in infarction, right	Lung abscess	No significant abnormality	Thrombophlebitis, right leg and femoral vein. Pulmonary emboli and infarct	Chest pain	
12	M	56	Right and left	Pulmonary tuberculosis, far-advanced	Pulmonary tuberculosis	Cor pulmonale	None	Marked dyspnea	Pulmonary sclerosis, marked
13	M	66	Left	Lung cyst, right; tuberculosis, far-advanced, left	Pulmonary tuberculosis	No significant abnormality	None	Marked dyspnea	Continuous hospitalization for over 10 years. Respiratory cripple for two years before death
14	F	59	Right	Metastatic carcinoma	Disseminated breast carcinoma	No significant abnormality	Multiple pulmonary emboli	Dyspnea and cyanosis	Widespread metastases

TABLE 1—*Continued*

Case No.	Sex	Age, yrs.	Main Pulm. Art. Involved	Pulmonary Disease	Associated Main Path. Diagnosis	Hear	Other Thrombo-emb. Phenomena	Outstanding Symptoms	Additional Features
15	M	58	Right	Bronchiectasis, pulmonary fibrosis and emphysema	Same	Cor pulmonale and left ventricular hypertrophy	Previous pulmonary emboli (clinical)	Progressive dyspnea, cyanosis	EKG change of axis of heart; secondary polycythemia, marked
16	M	81	Right	Pulmonary edema	Coronary occlusion	Myocardial infarction	Coronary thrombosis, recent embolus and infarct, right lower lobe	Chest pain, shock	Coronary sclerosis
17	M	52	Main trunk, right and left	Pulmonary tuberculosis, far-advanced	Pulmonary tuberculosis	Hypertrophy of left ventricle and pulmonary conus	None	Dyspnea	Marked mediastinal shift
18	M	15 months	Right and left	Bronchopneumonia	Tetralogy of Fallot	Tetralogy of Fallot	None	Dyspnea and cyanosis	Youngest case on record
19	F	67	Right and left	None	Massive pulmonary thrombosis, hypertensive heart disease	Hypertrophy of both ventricles, dilatation of right	Thrombophlebitis of both legs and iliac veins	Dyspnea	
20	F	78	Left	Small peripheral infarct	Arteriosclerotic heart disease	Left ventricular hypertrophy	Segmental infarct, left lung; thrombosis, left auricular appendage	Mental confusion	Generalized arteriosclerosis
21	M	78	Right and left	Emphysema, bronchiectasis, RLL bronchopneumonia and infarct	Massive pulmonary embolus and thrombosis	Left ventricular hypertrophy, right heart hypertrophy, pulmonary conus dilatation	Infarction, R.L.L. thrombosis, right carotid artery and left popliteal vein	Dyspnea	Thrombophlebitis, left leg; embolus with superimposed thrombosis

monary circulation has a great reserve, with the ready distensibility of the smaller vessels and the large number of reserve capillaries through which blood does not ordinarily flow. In addition to these features, the development of anastomotic channels between the pulmonary and bronchial arterial branches may provide considerable collateral circulation. Thus it may be that a small chink is all that remains to sustain life, and it is probably the final obliteration of this chink which causes death in many instances.

Incidence

The incidence of massive pulmonary thrombosis is quite low. In the review herewith presented there were 21 cases in 11,511 consecutive autopsies, an incidence of 0.18%. In 1921 Billings [2] noted 11 cases in 1,700 autopsies, an incidence of 0.7%, and in analyzing 6,200 autopsies from various sources he found 16 cases, an incidence of 0.26%. In 1934 Kampmeier [3] collected 23 cases from the literature and also reported one of his own. The same year Fowler [4] reported six cases in 935 consecutive autopsies at the University Hospital at Iowa City, and also tabulated a total of 62 cases from the literature, including foreign sources. In 1941 Savacool and Charr [5] reported 12 patients with pulmonary tuberculosis who showed massive thrombosis of the pulmonary artery at autopsy. It should be noted, however, that four of their 12 cases showed thrombosis of one or more lobar branches only, and were not pulmonary artery or right or left main branch thromboses. In the same article they also review the literature of the period from 1837 to 1940, and tabulated a total of 88 cases reported by 52 authors. Here, too, it should be noted that 18 of these 88 cases were instances of lobar involvement only. Carroll [6] reported on five cases in 1950, four diagnosed post mortem, and one in which an exploratory thoracotomy was done and a biopsy of the pulmonary artery was made. Reference to his article will be made subsequently in a discussion of present-day methods of diagnosis. In 1951 Hamelin and Eyler [7] reported on five cases, with emphasis on specific roentgen manifestations. During the same year Kyser,[8] in a review of the autopsy material at the Evanston Hospital in Illinois, reported 14 cases in the 10 year period 1940 to 1949. Seven cases with necropsy studies are also reported in a fairly recent article by Keating et al.,[22] with particular note on the x-ray findings.

Sporadic cases have been noted by many authors from 1929 to the present. These include Barnes and Yater,[9] Jump and Baumann,[10] Boswell and Palmer,[11] Means and Mallory,[12] Massachusetts General case reports,[13] Schneider and van Ordstrand,[14] Bryson,[15] Conklin and Litwin [16] and Canada et al.[17]

Etiology

The cases of massive pulmonary thrombosis may be divided into two main groups: (1) those superimposed upon a previous pulmonary embolus, and (2) those arising in situ without any previous embolic episode, and hence

autochthonous. It is most difficult to attempt differentiation of these two types by pathologic study alone; hence, in most cases one can only attempt differentiation by the clinical picture and the associated postmortem findings. In our series of 21 cases we could state with a fair degree of certainty that the pulmonary thrombus was superimposed upon a previous embolus in six instances (cases 11, 14, 15, 16, 19 and 21). In the remaining cases we cannot be certain, but can only assume that in a fair percentage of these the thrombosis was autochthonous in view of the lack of any contrary evidence.

The pathologic processes most often found in association with massive pulmonary thrombosis include chronic pulmonary disease and chronic heart disease. As emphasized by Bryson,[15] "Chronic pulmonary disease will predispose to the development of pulmonary artery thrombosis by two methods: First, the chronic disease by destroying the lung and capillary tissue ultimately increases the pulmonary arterial pressure and thus influences the development of arteriosclerosis which in turn damages the vessel wall. Secondly, the chronic disease by causing obliterative endarteritis slows pulmonary circulation and thus influences the blood coagulation." There was severe chronic pulmonary disease in 15 of our 21 cases. Seven of these had far advanced pulmonary tuberculosis, five pulmonary fibrosis and emphysema, and one a chronic lung abscess; two additional cases had involvement of the lung by carcinoma, one primary and one metastatic. In all cases of unilateral thrombosis, chronic pulmonary disease, if present, was on the same side.

In chronic heart disease, particularly with heart failure, the resultant chronic passive congestion of the lungs offers a good breeding ground for thrombosis, particularly in the presence of a cor pulmonale. In this connection, it is also interesting to note recent reports on the association of thrombosis of the pulmonary artery with defects of the interarterial septum.[17, 18] In the article by Canada et al.[17] it is pointed out that, although the defect predisposes the pulmonary artery to thrombus formation, it may also provide the means for survival after an obliterating thrombosis has developed.

Nonpenetrating chest trauma as a possible contributing cause to pulmonary thrombosis in a case with a widely patent foramen ovale is reported in a recent article by Dimond and Jones.[19]

As shown by Brenner,[1] autochthonous thrombi may also result from localized disease of the pulmonary arterial wall, such as congenital or luetic aneurysms of the pulmonary artery, acute pulmonary arteritis due to local disease of the surrounding lung or complicating the pathology of ductus arteriosus, and in syphilitic arteritis. The luetic conditions of the pulmonary artery, however, are relatively rare entities today.

Clinical Picture

The clinical picture of pulmonary thrombosis is often masked by the underlying and complicating lesions of the lungs or heart, and this un-

doubtedly accounts for the usual difficulty in antemortem diagnosis. However, there are certain features of the clinical picture, together with the newer diagnostic methods mentioned below, which should make clinical diagnosis more frequent than heretofore.

Dyspnea is usually the outstanding symptom, and this has been emphasized by many authors.[2, 12, 13, 20] The dyspnea is usually severe. This was notable in 17 of our 21 cases. It is also not explainable by the usual causes, being more marked than would generally be expected by the amount of cardiac or pulmonary pathology present. In many instances, another unusual aspect of the dyspnea is the fact that the pulmonary fields may appear relatively clear, and there may be little evidence of pulmonary congestion despite widespread evidence of heart failure. Finally, it is usually intractable despite therapy, and slowly and unremittingly progressive.

Cyanosis is usually marked and also a prominent feature. It was present in most of our cases, and particularly severe in six.[2, 5, 8, 14, 15, 18] Like the dyspnea, it is more marked than the underlying pulmonary or cardiac disease would seem to warrant.

Other symptoms which may be present include cough and thoracic or epigastric distress. Middleton [21] describes excruciating abdominal pain as an "unusual and startling manifestation" of pulmonary thrombosis, and ascribes it to a vagus reflex. Restlessness and mental confusion may occur because of relative cerebral anoxia. Savacool and Charr [5] mention the presence of blurred vision, exophthalmos and conjunctival congestion due to edema of the retrobulbar tissues and retinal congestion.

Most patients develop evidence of right heart hypertrophy with subsequent right heart failure due to cor pulmonale. This is often the mode of death. It is notable that six cases in the series had definite cor pulmonale post mortem, and in eight others there was evidence of some degree of right heart hypertrophy or dilatation.

Diagnosis is difficult, but recent emphasis on additional diagnostic aids with x-ray, angiocardiography and cardiac catheterization should be of considerable help. The roentgen manifestations of pulmonary thrombosis are well described by Hamelin and Eyler [7] and Keating et al.[22] In the hilar region an abnormal hilar mass due to enlargement of the pulmonary artery may be seen. In addition, because of the obstruction, the lung fields appear abnormally radiable, with an absence of vascular markings. On fluoroscopy there may be absent hilar pulsation on the involved side. Angiocardiography is an excellent method for confirming the presence of pulmonary obstruction when massive thrombosis is suspected. Finally, if right heart catheterization is done, the presence of high right ventricular pressure with a low cardiac output may be found. These new diagnostic procedures are described by Carroll.[6] Right heart catheterization was employed in two cases and angiocardiography in one of the five cases of his series.

Treatment

Heretofore, the treatment of massive pulmonary thrombosis has been of academic interest only, inasmuch as antemortem diagnosis was such a rarity. However, it is probable that this diagnosis will be made clinically with greater frequency in the future. In addition to the treatment of the underlying disease, the chief consideration is whether the continued use of anticoagulants may prevent further propagation of the clot. As noted, the pulmonary vasculature has a tremendous reserve, and the maintenance of only a small lumen may prolong life for a reasonable period. In view of the dire prognosis, it is certainly worthy of a prolonged trial.

Case Reports

Case 1. A 26 year old single male was admitted to Queens General Hospital on August 16, 1940. Five years prior to admission he had been hospitalized at Seaview Hospital for tuberculosis but had signed out after one month. He was then followed in a Department of Health Clinic and thought he was getting on fairly well until he had a bout of hemoptysis two days prior to admission.

On admission he appeared acutely ill and febrile, and showed evidence of advanced pulmonary tuberculosis on the right. He was markedly dyspneic. He ran a continuously febrile course, and successive x-rays showed acute extension of the tuberculous infiltration in the left lung. Toxemia and intractable dyspnea persisted, and he died on September 23, 1940.

On autopsy the right main pulmonary artery contained an adherent, laminated, grayish red thrombus. On section, opaque yellowish tissue was noted where the thrombus was adherent to the intima. The left main pulmonary artery also contained a grayish red thrombus which appeared well laminated and incompletely occluded the lumen. This thrombus extended down to the left lower branch.

There was bilateral advanced tuberculosis with cavitation and disseminated caseous foci. On the right there was also a massive infarct with secondary infection. The heart showed cor pulmonale.

Comment: In this instance pulmonary thrombosis was superimposed on chronic pulmonary disease. The extreme dyspnea is readily understandable in the face of the marked destruction of pulmonary parenchyma, as well as the severe encroachment on the pulmonary circulation by the right and left main pulmonary artery thromboses.

Case 2. A 50 year old Negro male was admitted to Queens General Hospital on August 26, 1940, because of increasing dyspnea over a period of five months. On examination notable features were dyspnea, but not orthopnea, intense cyanosis of the upper part of the body, especially of the head and upper extremities, clubbing of the fingers and an enlarged liver. X-ray of the chest revealed an enlarged heart and bilateral cystic disease with emphysema. Additional findings were a 4 plus Kline test, an ether circulation time of 26 seconds with a saccharine time of 65 seconds, and a relative polycythemia. To some observers the clinical picture in many respects resembled Ayerza's disease, particularly because of the intense cyanosis. On October 9, 1940, the patient suddenly developed severe abdominal pain. His abdomen became boardlike, and he died the following day.

At autopsy death was found to be due to a mesenteric thrombosis with accompanying extensive infarction of the intestines. The lungs showed cystic disease and

chronic bronchiectasis, as well as pulmonary fibrosis and emphysema. There was arteriosclerosis of the pulmonary vessels. The left pulmonary artery contained a markedly adherent, large, grayish red thrombus, which extended down into some of the smaller ramifications. A similar thrombus was noted in the right pulmonary artery. No gross areas of infarction were noted in any portion of either lung. The heart showed evidence of both right and left hypertrophy. The coronaries showed moderate sclerosis, and there was a small recent infarction. Additional findings of note included thrombosis in the renal and splenic arteries, with old and recent infarctions in both of these organs, and luetic aortitis.

Comment: There are two particularly interesting aspects to this case. One was the intense cyanosis of the upper part of the body. The other was the rather widespread areas of arterial thrombosis besides that in the pulmonary artery. The mesenteric artery thrombosis precipitated his death.

Case 3. A 70 year old white male was admitted to Queens General Hospital on September 24, 1941, because of increasing dyspnea. He had been hospitalized for a period of six weeks about a year previously for congestive failure. He had also received treatment for syphilis previously. On examination he presented signs of right heart failure, with marked dependent edema, ascites and an enlarged liver. The clinical impression was that the patient had a cor pulmonale secondary to pulmonary fibrosis. The patient's course was downward, and he died on October 2, 1941, with signs of a terminal bronchopneumonia.

At autopsy the right main pulmonary artery was completely occluded by a laminated, adherent thrombus (figure 1). The thrombus extended proximally to a point 3 cm. above the pulmonary valve in the main pulmonary artery and distally to the tertiary ramifications. The left main pulmonary artery was patent throughout. No infarcts were visible in the right lung. Both main pulmonary vessels presented moderate arteriosclerotic changes. Both lungs showed bronchopneumonia and extensive fibrosis with widespread induration. The heart was moderately enlarged, with right ventricular hypertrophy and dilatation. The right ventricular wall was 1 cm. in thickness. The coronary vessels showed minimal sclerosis. There was also a recent thrombus in the right auricular appendage.

Comment: In addition to the usual association of cor pulmonale with pulmonary thrombosis, this case also well illustrates the absence of pulmonary infarction in the face of a slowly forming massive pulmonary thrombosis.

Case 4. An 89 year old white female was admitted to Queens General Hospital on June 24, 1942, because of drowsiness, inability to eat and semistupor. She had had a three month history of dyspnea on exertion and had been on digitalis therapy.

On examination she appeared poorly nourished, slightly cyanotic and somewhat dehydrated. Cheyne-Stokes respiration was noted. The heart was enlarged and fibrillating. There was no peripheral edema. She was treated with digitalis and general supportive measures, but died four days after admission. Clinical diagnoses included arteriosclerotic heart disease and cerebral thrombosis.

At autopsy the lungs showed bilateral lower lobe bronchopneumonia and congestion. Within both right and left main pulmonary arteries were moderately firm, adherent, grayish red clots about 4 cm. in length and 1.5 cm. in width. Microscopically the thrombus was proved to be antemortem, with early organization of the adherent edge. The heart weighed 400 gm., with some left ventricular hypertrophy. The valves were normal, and the coronary arteries showed minimal arteriosclerosis.

Comment: This is the oldest patient in the series, and one of the few who did not have underlying chronic pulmonary disease.

Case 5. A 48 year old female was admitted to Triboro Hospital on August 8, 1942, because of dyspnea and fever. Her illness dated back to 1934, when she was found to have pulmonary tuberculosis. She had been treated by a regime of bed-rest and then a right pneumothorax which was subsequently complicated by an empyema

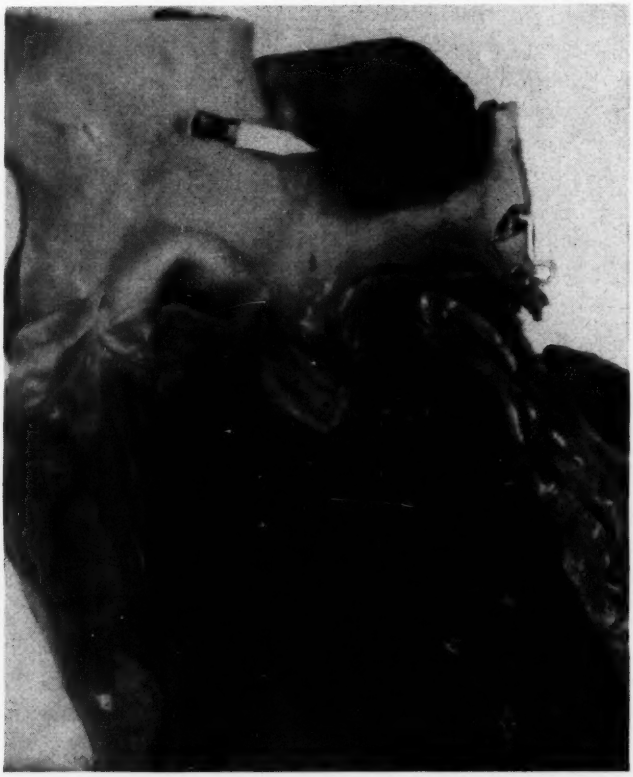

FIG. 1. *Case 3.* The right ventricle and pulmonary artery have been opened from the anterior aspect. Note the adherent laminated thrombus involving the main pulmonary artery, and the right ventricular hypertrophy and dilatation.

and so was discontinued in 1937. She did fairly well until September, 1941, when she developed dyspnea, edema, fatigability and fever, followed in April, 1942, by a rather severe bout of hemoptysis. On admission she was febrile, dyspneic and extremely cyanotic, with generalized anasarca. X-ray revealed a massive effusion on the right, and a linear, patchy infiltration on the left which appeared to shell out on subsequent films. Sputum was positive for acid-fast bacilli.

She remained toxic, dyspneic and cyanotic throughout her course, and during

the latter part of the illness developed increasing distention of her cervical and upper thoracic veins. She showed no response to cardiac and other supportive therapy, and died on October 6, 1942.

At autopsy far advanced bilateral pulmonary tuberculosis was found, with a massive right empyema and a huge cavity in the left upper lobe. The right lower and right middle pulmonary arteries were completely occluded at the hilum by an adherent thrombus, which presented fresher thrombotic propagation back into the right main pulmonary artery (figure 2). There was evidence of pulmonary arteriosclerosis microscopically. There was also thrombosis of the left innominate vein.

FIG. 2. *Case 5.* The lung and main pulmonary arteries are viewed from the anterior aspect. The thrombus occupies almost the entire lumen of the right main pulmonary artery.

The heart was markedly dilated, with particular dilatation of the right auricle and right ventricle, as well as right ventricular hypertrophy. There was an adherent mural thrombus in the right auricular appendage.

Comment: This case again illustrates the development of a failing cor pulmonale in the face of long standing chronic pulmonary disease. The severity of the dyspnea and the cyanosis and their intractability to therapy were outstanding clinical features. It is possible that the thrombosis in either the left innominate vein or the right auricular appendage may have been the nidus for propagation into the pulmonary artery.

Case 6. A 62 year old white male was first admitted to Triboro Hospital on June 9, 1943, because of chronic productive cough and wheezing of several years' duration, with recent exacerbation. During his hospital stay his cough was persistent, and his sputum was always blood-streaked. Repeated examinations for acid-fast bacilli were negative. Bronchoscopy showed a cauliflower mass in the right upper lobe bronchus, diagnosed as carcinoma, though a positive biopsy was not obtained. Surgery was advised, but on July 28, 1943, the patient signed himself out of the hospital.

He was readmitted on October 28, 1943, because of severe exacerbation of his symptoms and marked loss of weight. On examination he was extremely cachectic and dyspneic. Chest x-ray showed consolidation extending outward from the right hilus and a rounded density extending into the right main bronchus. His condition was stable for some time, but weakness, cough and dyspnea increased progressively. He died on April 10, 1944, 10 months after his first admission. Clinical diagnosis included carcinoma of the right upper bronchus, with atelectasis and bronchiectasis of the right lung due to obstruction by the neoplasm.

At autopsy the right main pulmonary artery revealed an adherent thrombus occluding the mouths of the upper two branches and hanging over the mouth of the right lower lobe artery. On microscopic examination this proved to be an antemortem thrombus. No tumor cells were seen in it. The main lesion was the anaplastic squamous cell carcinoma of the right upper lobe bronchus with complete obstruction. There were extension and replacement with tumor of almost the entire right upper lobe, with marginal atelectasis and chronic pneumonitis. There was purulent bronchiectasis of the entire right lung. There was tumor thrombosis of the pulmonary veins extending from the right upper lobe into the left auricle, and a huge ball valve thrombus in the left auricle. The heart weighed 280 gm., with right heart dilatation and coronary sclerosis.

Comment: The pulmonary artery thrombosis in this instance was probably formed in situ and secondary to the circulatory disturbances provoked by the pulmonary carcinoma. Of course, tumor thrombosis of the pulmonary artery is a recognized complication of bronchial malignancy, but there was no microscopic evidence of this here.

Case 7. A 31 year old Negro male was admitted to Queens General Hospital on June 2, 1946. He complained of a cough, intermittent right lower anterior chest pain, occasional night sweats, and a 10 pound weight loss over a three week period. Examination disclosed a well developed, well nourished Negro male who appeared acutely ill and dyspneic. Chest x-ray revealed a dense localized shadow at the right hilum compressing the bronchus. Examination of the sputum disclosed acid-fast bacilli.

On July 11, 1946, the patient was transferred to Triboro Hospital. There

bronchoscopy revealed a right lower lobe bronchial tuberculosis. His clinical course was septic. On July 22 a pericardial friction rub was heard, as well as a left pleural friction rub. The pulmonic second sound became louder than the aortic second sound. Sulfadiazine had no effect on the development of the pericardial lesion. Generalized lymphadenopathy developed. On August 3, 1946, the patient had an episode of sudden dyspnea and died in a period of several minutes.

Clinical diagnoses included acute miliary tuberculosis, tuberculous pneumonia, tuberculous pericarditis with effusion, and bilateral pulmonary embolism.

At autopsy the mediastinal lymph nodes were grossly involved in caseous tuberculosis. There was a right tuberculous bronchitis, and a lymph node had apparently ruptured into the bronchus. Bilateral tuberculous pleuritis was present. There were many small tuberculous foci scattered throughout both lungs. A small infarct which contained visible tubercles was found in the right lower lobe. A gray laminated but not completely occlusive thrombus was found in the right pulmonary artery. Microscopy of the pulmonary artery showed an arteritis with overlying thrombus partly organized adjacent to regional tuberculous mediastinal nodes.

The heart weighed 580 gm. There were left ventricular hypertrophy and right ventricular dilatation. Tuberculous pericarditis was seen grossly and microscopically. Miliary tuberculous foci were found in the myocardium and in the liver.

Comment: This patient was presumed to have a primary type of progressive disseminated tuberculosis. It is of interest that the pulmonary artery thrombosis was probably induced by the arteritis secondary to the caseous tuberculosis in the adjacent lymph nodes. The small peripheral infarct may have been due to embolization from the pulmonary artery thrombus.

Case 8. A 57 year old Negro female was admitted to Queens General Hospital on February 19, 1947. She had been in the hospital on two previous occasions: once in 1936 for the treatment of syphilis, and again in 1945 for pneumonia and heart disease. She had been on digitalis and had been followed in the Out-Patient Department for two years preceding the present admission.

On admission she presented evidence of cardiac failure with dyspnea, edema, enlarged liver, basal râles and distended neck veins. She was cyanotic and had marked clubbing of the fingers. The heart was enlarged and fibrillating. P-2 was loud, and there was a mumbling, low-pitched pulmonary diastolic murmur and accompanying thrill. Blood pressure was 160/100 mm. of Hg. The pulmonary conus was described as "tremendous," and a review of her x-rays over a period of years revealed increasing pulmonary fibrosis, especially on the left, as well as progressive enlargement of the right ventricle. The electrocardiogram was consistent with chronic cor pulmonale.

The patient was considered to have a failing cor pulmonale with pulmonary fibrosis. Because of the cardiac findings, other diagnoses considered were aneurysm and endarteritis obliterans of the pulmonary artery. In addition, because of the very pronounced pulmonary conus, the possibilities of interarterial septal defect and Eisenmenger's complex were also entertained.

She showed only a temporary response to usual cardiac therapy, and died on April 28, 1947.

At autopsy both ventricles were hypertrophied and dilated. However, the right ventricle varied from 5 to 9 mm. in thickness in various portions of the wall. The main pulmonary as well as the right pulmonary artery branches were markedly dilated. The left pulmonary artery was almost completely occluded by a fresh and also an organized and laminated thrombus measuring 2 cm. in thickness. To account for the cor pulmonale there were extensive pulmonary fibrosis and emphysema of

all lobes. There was also a recent infarct in the left lower lobe. Additional significant findings were an old infarction at the apex of the left ventricle and a thrombus in the right auricular appendage. Death was considered to be due to cor pulmonale and pulmonary thrombosis as well as to arteriosclerotic heart disease.

Comment: In retrospect the development of the cor pulmonale secondary to long-standing pulmonary disease as well as the subsequent massive pulmonary thrombosis appears fairly clear-cut. However, a baffling clinical feature during life was the loud pulmonic diastolic murmur. This apparently was due to pulmonary regurgitation in the widely dilated pulmonary artery.

Case 9. A 78 year old white female was first admitted to Queens General Hospital in March, 1947, and then again in April, 1947, for what was diagnosed as cholelithiasis and diverticulitis. Her final admission was on July 22, 1947. She had lower abdominal pain, with swelling of the abdomen and legs, but no cardiorespiratory symptoms. She was treated with digitalis and penicillin, but died on July 28, 1947. Clinical diagnosis was ovarian carcinoma with metastases.

At autopsy an antemortem adherent thrombus was found in the right pulmonary artery. There were pulmonary edema and congestion and very minimal tuberculosis. The main pathology was an adenocarcinoma of the fundus uteri, with metastases to omentum and peritoneum, and a serosanguineous ascites of at least 3,000 c.c. The heart weighed 400 gm. and showed left ventricular hypertrophy and right heart dilatation. In addition, she had chronic cholecystitis and cholelithiasis, and diverticulosis of the large bowel.

Comment: Factors contributing to the formation of the pulmonary thrombus in this case probably were the debilitation and cachexia associated with her malignancy.

Case 10. A 46 year old white female was admitted to Triboro Hospital on August 6, 1947, because of cough and weight loss over a period of six months. In 1940 pulmonary tuberculosis had been diagnosed after a pleurisy and pneumonia, and a pneumothorax was unsuccessfully attempted. On admission she was emaciated, and x-ray revealed far-advanced bilateral pulmonary tuberculosis with extensive cavitation on the right and atelectasis and bronchiectasis on the left. Sputum was positive for acid-fast bacilli with a high Gaffky count. Her course was progressively downhill. During the last two months of her life marked dyspnea was outstanding, and she was kept on continuous nasal oxygen. She died on September 22, 1948.

At autopsy there was extensive cavitation throughout the upper half of the right lung, while the lower half showed many discrete areas of bronchopneumonia. The left lung was markedly shrunken and contracted and weighed only 200 gm. There was a large adherent thrombus in the left pulmonary artery. There was no cardiac hypertrophy.

Comment: In this instance thrombosis developed in the pulmonary artery supplying a markedly shrunken and atelectatic left lung, the site of an old fibrotic tuberculosis with extensive secondary bronchiectasis.

Case 11. An 82 year old short and obese white female was admitted to Queens General Hospital on August 6, 1949, with fever and pleuritic chest pain of five days' duration. On examination dullness and crepitant râles were found over the upper right chest. She was first thought to have pneumonia, and had some favorable

response to penicillin. However, on August 18, 1949, she had a sudden episode of shock associated with cyanosis and dyspnea, followed later by hemoptysis. It was then recognized that she probably had recurrent pulmonary embolism. This was further confirmed by subsequent clinical evidence of thrombophlebitis in the right leg. She failed to respond or improve with anticoagulants and cardiac supportive therapy. Her course was toxic, and she died rather suddenly on September 5, 1949.

Autopsy revealed the right lung to contain a large, pus-filled cavity occupying most of the right upper and middle lobes. The right pulmonary artery contained a large old grayish white thrombus, completely occluding the lumen and firmly adherent to the wall.

When the right deep femoral vein was milked a large antemortem thrombus was extruded.

Comment: This is a classic case of pulmonary embolization secondary to thrombophlebitis of the extremities in an elderly woman. The pulmonary thrombosis was undoubtedly superimposed on the antecedent embolus, with subsequent organization and fibrosis. The breakdown of an infarct into an abscess is not very common, but this secondary infection is understandable in a feeble and devitalized old lady.

Case 12. A 56 year old white male was admitted to Triboro Hospital on April 30, 1951, in critical condition and extremely dyspneic. He had had known pulmonary tuberculosis since 1937, and had been treated at various institutions as well as at home. X-ray revealed bilateral, far advanced caseous pulmonary tuberculosis with bilateral cavitation. Despite the advanced nature of his pulmonary disease, it was not considered to be solely responsible for his severe dyspnea, which was unrelieved by oxygen. He was thought to have a complicating chronic cor pulmonale, and this was partially borne out by evidence of an enlarged heart on x-ray and the electrocardiogram, which revealed definite right heart strain. Extreme dyspnea remained his outstanding symptom, and he died on May 17, 1951.

Postmortem examination revealed that both the right and the left main pulmonary arteries contained old and well organized thrombi which were firmly adherent to the walls. In the smaller branches of the pulmonary arteries there were more recent thrombi. The pulmonary arteries also showed a considerable amount of sclerosis, and near their point of origin from the pulmonary conus there were aneurysmal-like dilatations on either side.

The heart was markedly enlarged, with considerable dilatation and hypertrophy of the right ventricle and a much lesser involvement of the left ventricle. There was also marked coronary sclerosis.

Death was considered to be due to pulmonary thrombosis in a patient with far advanced pulmonary tuberculosis and chronic cor pulmonale and arteriosclerotic heart disease.

Comment: The long-standing chronic pulmonary disease probably led to pulmonary sclerosis, and this in turn provided further basis for the development of the widespread pulmonary thrombosis noted at autopsy. The clinical picture of advanced pulmonary tuberculosis was clouded by the associated cor pulmonale and pulmonary thrombosis. Intractable dyspnea, out of proportion to the amount of pulmonary disease present, was the outstanding symptom.

Case 13. A 56 year old white male, a private chauffeur, was admitted to Triboro Hospital on June 10, 1941, and remained as a patient at the institution

continuously until his death on October 26, 1950. He apparently had been entirely well until two years prior to admission. At that time he developed blood-streaked sputum following an accident in which there was chest trauma. X-rays shortly afterward were presumably negative, but almost a year later, after a bout of hemoptysis, another x-ray revealed a tuberculous lesion in his left apex and a large bullous cyst occupying the middle third of his right lung. He was admitted to another institution, where an attempt was made to needle the cyst and instil Lipiodol. However, the patient developed a spontaneous pneumothorax which required thoracotomy and tube drainage.

The patient was transferred to Triboro Hospital on June 10, 1941. At that time his general condition was good and he presented only dyspnea on exertion. During the following nine years there was a slow but inexorable extension of the area of the cyst on the right and of the tuberculous process on the left. With this gradual and persistent impingement on residual functioning pulmonary tissue, the patient became progressively more dyspneic. During the last months of his life this dyspnea was severe even at complete rest and with the continuous use of oxygen.

For the last two or more years of this patient's life he was a respiratory cripple, and was able to remain alive only by virtue of continuous supportive treatment in the sheltered atmosphere of the hospital. Eventual death on October 26, 1950, was due to respiratory failure at the age of 66.

At autopsy the right lung appeared to be practically a huge sac. The left lung was fibrotic, firm and markedly compressed. In the left upper lobe was a large cavity which communicated with the pleural cavity and formed a sacculated empyema measuring approximately 5 cm. in diameter. The left main pulmonary artery contained a firm, red-gray laminated thrombus. Both pleural cavities were completely obliterated by dense fibrous adhesions. Additional findings of note were coronary sclerosis and myocardial fibrosis. The heart weighed only 220 gm., and there was no hypertrophy of either ventricle.

Comment: One remarkable aspect of this case is the fact that this patient survived as long as he did in view of the small remaining amount of functioning pulmonary tissue. The cyst had obliterated most of the lung parenchyma on the right, and the tuberculous involvement on the opposite side with accompanying cavitation, fibrosis and atelectasis left little functioning parenchyma here. Superimposed on this was the presence of the organized thrombus in the left main pulmonary artery. He probably survived as he did only because he was in the sheltered atmosphere of a hospital continuously for over 10 years. This case is an excellent example of the development of massive organized pulmonary thrombus in association with chronic pulmonary disease.

Case 14. A 59 year old white female was admitted to Queens General Hospital on May 4, 1952, in a semicomatose condition. Two years prior to admission the patient had had a radical mastectomy for carcinoma of the right breast at Memorial Hospital. One year later a right radical neck dissection was done. For several weeks before admission the patient had been suffering from shortness of breath and blood-streaked sputum, and had been confined to bed for six months prior to admission. A few hours before admission the patient had had an attack of sharp, pressing precordial pain, followed by severe dyspnea and cyanosis.

On physical examination the patient appeared cyanotic and was semicomatose. There was evidence of tumor recurrence in the neck scar and a mass was palpated in the left breast. She was treated with digitalis and antibiotics. She did satis-

factorily at first, but on May 16, 1952, she had another episode of cyanosis and dyspnea, and died. Clinical diagnosis was metastatic carcinoma.

At autopsy the right pulmonary artery contained an adherent thrombus almost completely occluding the lumen. On the left, some of the smaller branches of the pulmonary arterial tree were similarly occluded. The lung parenchyma showed scattered metastases from the scirrhous adenocarcinoma of the breast, as well as pleural involvement at the right apex and left base. The mediastinal lymph nodes also had tumor metastases. There was scirrhous adenocarcinoma involving the left breast, with axillary node involvement and metastases to ribs and vertebra.

Comment: The clinical history in this case suggests episodes of pulmonary embolization followed by thrombosis. Additional factors predisposing toward thrombosis were the pulmonary metastatic involvement and the prolonged period of confinement to bed in a cachectic state.

Case 15. A 58 year old white male was admitted to Queens General Hospital on October 5, 1952. He had originally been seen in January, 1947, because of dyspnea, hypertension, marked cyanosis and obesity. The hemoglobin was 21 gm.; hematocrit, 67%. Diagnoses were secondary polycythemia and bronchiectasis. He was re-admitted twice in the fall of that year because of precordial pain and syncope. Electrocardiogram showed left axis shift and coronary insufficiency. He was treated in the hospital and the clinic with phlebotomies and digitalis. In 1950 the patient was admitted six times for dyspnea, weakness, recurrent thrombophlebitis, small pulmonary infarcts and plethora. On all admissions chronic productive cough and cyanosis were present. He was treated variously with phlebotomies, antibiotics, anticoagulants and digitalis. An electrocardiogram late in 1950 showed a vertical axis. He was managed for several years in the clinic. For several weeks before his admission in October, 1952, the patient had suffered from increasingly severe dyspnea. On examination he was found to be obese, cyanotic, dyspneic and plethoric. The sclerae were congested and the neck veins distended. There was a harsh systolic murmur over the precordium. The fingers were clubbed. He was treated with digitalis, morphine and mercurials, but died the same day. The clinical diagnosis was myocardial infarct with acute pulmonary edema.

At autopsy, in the right pulmonary artery, 1 cm. distal to the bifurcation, there was a firm, adherent, partly organized antemortem thrombus which almost completely blocked the lumen. It also extended down into the smaller ramifications of the artery. The lung parenchyma showed bronchiectasis of both lower lobes, with severe fibrosis and emphysema involving all lobes. There was no edema, congestion or infarct grossly or microscopically. The heart weighed 600 gm. There was marked dilatation of the right ventricle, with moderate hypertrophy, and also some dilatation and hypertrophy of the left ventricle.

Comment: The significant factors in this case are the history of previous thrombo-embolic phenomenon, and the presence of chronic pulmonary disease with severe polycythemia. The final episode is explained by the failing cor pulmonale and, of course, the pulmonary artery thrombosis.

Case 16. An 81 year old white male was admitted to Queens General Hospital on December 13, 1952, in extremis. He had been in cardiac failure for one year and was being treated with digitalis and mercurials. He had been ambulatory until December 9, 1952, when he suddenly complained of epigastric, chest and shoulder pain. This subsided and he remained ambulatory. On the day of admission, however, he became very weak and was brought to the hospital. On examination he was markedly dyspneic and cyanotic and in shock. Bubbling râles were heard

throughout the lungs. He died 90 minutes after admission. Clinical diagnosis included myocardial infarction and pulmonary edema.

At autopsy the heart weighed 500 gm. Both right and left ventricles were moderately hypertrophied, and the myocardium was flabby. The coronary arteries were sclerotic, and fairly fresh occlusions were found in the left anterior descending and the left circumflex coronary arteries. The right pulmonary artery showed an old massive antemortem thrombus which occupied approximately three quarters of the vessel lumen, extending distally about 3 cm. A small artery in the right lower lobe contained a fresh antemortem thrombus, distal to which there was an area of acute infarction. The artery of the left upper lobe was occluded by an adherent thrombus 1 cm. in length. The left lower lobe artery had a similar old thrombus occluding the lumen. Pulmonary edema was present.

Comment: This case illustrates how advanced the pulmonary artery thromboses may be and still be apparently asymptomatic. The distal pulmonary infarct may have been due to embolization from the main thrombus. It is of interest to note again the absence of massive infarct in a proximal main arterial occlusion and the presence of a peripheral infarct with a distal occlusion.

Case 17. A 52 year old white male was admitted to Triboro Hospital on June 18, 1953. His pulmonary tuberculosis had first been discovered in 1941, and he had been treated in Metropolitan Hospital until 1947. During this period he had had very frequent asthmatic attacks. He was discharged with a negative sputum in 1947. In November, 1952, the patient had hemoptysis, but delayed hospitalization until June, 1953. Chest x-ray showed far advanced caseous tuberculosis throughout the left lung field, with many areas of cavitation and infiltration in the right upper lobe. Sputum examination showed acid-fast bacilli. His general condition was poor, and he was intermittently dyspneic and semiconscious for most of his hospital stay. He died on July 11, 1953. Clinical diagnoses were bilateral, far advanced pulmonary tuberculosis and endobronchial tuberculosis.

At autopsy an antemortem thrombus was found in the main pulmonary artery, with extension along the left and right main arteries and to the artery of the right upper lobe. There were a bilateral chronic adhesive pleuritis and bilateral, far advanced fibrocaseous pulmonary tuberculosis. The left lung was partly collapsed and small, with marked fibrosis and moderate bronchiectasis. The mediastinum and right lung were shifted toward the left. The right lung showed emphysema and many caseous foci. The heart revealed left ventricular hypertrophy and dilatation of the pulmonary conus.

Comment: The rôle that chronic mediastinal shift may have had in fostering pulmonary artery thrombosis in this case is a matter for speculation. Otherwise, this case is another instance of massive thrombosis occurring with long-standing pulmonary disease.

Case 18. A 14 month old white male infant was admitted to Queens General Hospital on July 22, 1954, because of cyanosis and dyspnea. He had been admitted to other hospitals three times in the previous year for similar attacks. Marked polycythemia had also been noted at a former institution. Physical examination revealed the baby to be cyanotic, with clubbed fingers. The heart rate was rapid, with a "tic-tac" rhythm and with enlargement to both the right and the left. The lungs were clear. He was placed in an oxygen tent, with some relief of the dyspnea. Fluoroscopy and chest x-ray showed a globular heart, with right ventricular enlarge-

ment and well aerated lungs. An electrocardiogram showed sinus tachycardia and evidence of right ventricular hypertrophy. After one week the patient required oxygen only intermittently, and he was also given digitalis. On August 18, 1954, he developed a bout of severe dyspnea and tachycardia, deepening cyanosis and a fever of 104° F. Despite vigorous therapy he died on August 21, after three days of signs of increasing congestive failure. Clinical diagnosis was congenital heart disease, probably tetralogy of Fallot, with cardiac failure.

At autopsy the baby weighed 7,150 gm. The heart weighed 60 gm., and a typical tetralogy of Fallot was present, including partial stenosis of the pulmonary artery, hypertrophied right ventricle, high interventricular defect 1 cm. in diameter, and dextroposition of the aorta. Just above the main pulmonary artery the lumina of both the right and left branches of the pulmonary artery were occluded by an antemortem thrombus which extended a short distance into a patent ductus arteriosus. The lungs showed no infarction, but bronchopneumonia was present.

Comment: From the literature we reviewed, this is the youngest case of pulmonary thrombosis on record. The factors which tended to promote thrombosis in this infant with a tetralogy of Fallot were the lessened pulmonary flow because of the pulmonic stenosis and the polycythemia.

Case 19. A 67 year old obese white female was admitted to Queens General Hospital on October 1, 1954, because of progressive dyspnea of four days' duration, accompanied by distention of the face veins. Prior to that she had also noted some weakness of the left leg, with swelling. On examination she was severely dyspneic, although the chest was clear to auscultation. The heart tones were poor, and the pulmonic second sound was louder than the aortic. Chest x-ray revealed the heart to be transversely enlarged; the lung fields appeared clear. Despite therapy the patient's dyspnea persisted and she died the day following admission. Clinical diagnoses were hypertensive heart disease and pulmonary embolus.

At autopsy both right and left main pulmonary arteries were completely occluded by an antemortem adherent thrombus. There was also a small bit of what appeared to be more recent thrombosis. The thrombus filled most of the vessels and branched well into the hilar regions. The lungs showed no abnormality. Laminated antemortem thrombi were also found in both iliac veins, the larger on the left. The heart weighed 460 gm. The right atrium was dilated and the right ventricle was hypertrophied, along with a dilated pulmonary conus. The left ventricle was also hypertrophied, and the myocardium showed some fatty infiltration.

Comment: This case presented the clinical picture of progressive dyspnea. Pulmonary thrombosis was presumably secondary to previous embolization from the iliac vessels.

Case 20. A 78 year old female was admitted to Queens General Hospital from a convalescent home on October 29, 1954. Very little medical history could be obtained because of the confused and disoriented state of the patient. She was markedly undernourished and dehydrated, with pitting edema of the lower extremities and the left arm. There was a decubitus ulceration of the back. Despite attempts at hydration and nourishment by hypodermoclyses and nasogastric feedings she showed little response, became increasingly confused and died on November 13, 1954.

At autopsy there was a massive complete thrombotic occlusion of the left pulmonary artery (figure 3). The thrombus was gray in color and adherent to the wall of the vessel. There was a small peripheral infarct in the left lung. There was evidence of severe generalized arteriosclerosis, more notable in the aorta and iliac and renal arteries. However, coronary sclerosis was only mild. The left

FIG. 3. *Case 20.* Complete occlusion of the left main pulmonary artery is seen in this specimen, viewed from the anterior aspect.

ventricle was hypertrophied, and there was a thrombus in the left auricular appendage. Death was considered to be due to arteriosclerotic cardiovascular disease with failure, as well as pulmonary thrombosis.

Comment: In this elderly female there were probably several factors which contributed to the development of pulmonary thrombosis. These included pulmonary congestion, as well as dehydration and marasmus, which tended to increase blood viscosity.

Case 21. A 78 year old white male was admitted to Queens General Hospital on November 24, 1954, in acute respiratory distress. He had first been seen at this hospital in April, 1954, because of congestive heart failure and bronchopneumonia. Some pulmonary fibrosis had been noted on chest x-ray at that time. On his admission in November, 1954, the patient complained of increasing dyspnea for two weeks prior to admission. On examination he appeared acutely dyspneic and was coughing and wheezing. He was thought to have a thrombophlebitis of the left popliteal vein. His condition did not improve on a cardiac régime with antibiotics, and he died on December 9, 1954. Clinical diagnoses were arteriosclerotic heart disease in failure, bronchopneumonia and thrombophlebitis of the left leg.

At autopsy both right and left main pulmonary arteries were occluded by antemortem adherent thrombi. These were composed mainly of an embolic clot which was thought to have been present at least two weeks. Overlying this was a built-up thrombus, formed in situ as evidenced by clearly visible lines of Zahn which were oriented to the flow of the blood stream. The left popliteal vein showed thrombophlebitis. The right lower lobe had severe bronchopneumonia, with several areas of peripheral infarction. There were also moderately severe emphysema, minimal bronchiectasis and pulmonary congestion and edema. The heart weighed 400 gm. and showed slight hypertrophy of both ventricles. Dilatation of the pulmonary conus was seen, as well as some coronary sclerosis. There was generalized arteriosclerosis, with an old arteriosclerotic occlusion of the right main carotid artery and partial thrombosis of the splenic and mesenteric arteries.

Comment: This case is a typical example of pulmonary thrombosis superimposed upon a previous pulmonary embolus.

Discussion

As this series indicates, chronic thrombosis of the main pulmonary artery or the right or left main branch is a relatively rare postmortem finding and, moreover, is usually not diagnosed clinically. It is more apt to occur in the later decades of life, although the infant of 15 months with a tetralogy of Fallot provided the rare exception to this observation. There was no notable sex predominance. The predominance of right-sided thrombosis is interesting. Thus in our series there were nine in the right pulmonary, four in the left, and eight in both. The bilateral cases may have begun on the right. Savacool and Charr [5] also noted this right predominance, and explained it by the fact that the pulmonary artery was "squeezed" between the vein and bronchus on this side, while it was free on the left.

Most authors have been of the opinion that the majority of cases of pulmonary thrombosis are superimposed upon a previous embolus. We

would be reluctant to dispute this on the basis of our series of cases, despite the fact that in only six cases could we be fairly certain that this had occurred. However, in this connection it is interesting to note that eight of the remaining 15 cases had other thrombo-embolic phenomena, as noted in the table. It should also be noted that three of the eight cases in this group had mural thrombosis of the right auricular appendage. The thrombus in the appendage may have served as the nidus for propagation into the pulmonary artery in these instances.

Despite massive thrombosis, there is a notable absence of any massive infarction. This is undoubtedly due to the well known anastomoses between the pulmonary and bronchial arteries. This has been particularly well demonstrated experimentally by Bloomer et al.[23] They showed a "great and rapid rise in the amount of blood circulating through the bronchial arteries in the dog after ligation of the pulmonary artery." Liebow et al.,[24] by anatomic studies on injected postligation specimens, showed the relatively rapid expansion of anastomotic channels between the bronchial arteries and the pulmonary artery. Only seven of our 21 cases showed evidence of any pulmonary infarction, and in each instance the infarction was less than lobar in extent. In these instances the involvement of the peripheral vessel may have been due to embolization preceding the pulmonary thrombosis or to peripheral propagation from the already formed pulmonary artery thrombus.

As previously noted, most observers have found either chronic pulmonary disease or chronic heart disease in association with pulmonary thrombosis. Our series is noteworthy because of the rather marked predominance of chronic pulmonary disease in 15 of the 21 cases. The chronic pulmonary pathology probably led to a more sluggish circulation in the affected areas because of associated obliterative endarteritis. In addition, with long-standing pulmonary involvement there was also the frequent development of a cor pulmonale and associated pulmonary hypertension, with subsequent right heart failure. This provided another aggravating factor to favor pulmonary thrombosis. A third factor favoring thrombosis in these cases with chronic pulmonary disease was the frequent association of a secondary polycythemia.

In only four of our patients (cases 4, 16, 18 and 20) was there chronic cardiac disease not associated with underlying chronic pulmonary pathology. In many previously reported cases, primary cardiac disease was more frequent than this. Noteworthy, too, is the absence of any cases of mitral stenosis in our series.

One must also not lose sight of the fact that the pulmonary artery carries venous blood, hence the increased clotting tendency throughout the pulmonary arterial vasculature.

With regard to diagnosis, it is apparent from our series that this is difficult because the underlying pulmonary or cardiac pathology usually

masks the clinical picture. However, one diagnostic clue was the severity of the dyspnea, and the additional fact that it was usually more marked than the existing pulmonary or cardiac disease seemed to warrant. This was notable in most of our cases, as was the fact that the dyspnea was generally progressive and refractory to the treatment. Similarly, cyanosis, especially of the upper portion of the body, may be outstanding and, as previously noted, was particularly severe in several of our cases. The x-ray may be helpful by revealing hilar enlargement and an abnormally radiable pulmonary field. Fluoroscopy may reveal the absence of pulmonary pulsation on the involved side. The most valuable procedure, and one which will confirm the diagnosis of pulmonary thrombosis, is angiocardiography. This will graphically demonstrate the absence of filling of the pulmonary artery on the thrombosed side. Angiocardiography is a diagnostic aid which is being employed with greater frequency in recent years and which should make the clinical diagnosis a much more frequent occurrence.

Another clinical feature that the series emphasizes is that the end picture in many of these cases is that of a chronic cor pulmonale and its associated right heart failure. In several instances the clinical diagnosis of cor pulmonale was made without recognition of the underlying pulmonary thrombosis.

Note should be made of the fact that the appearance of the occluded pulmonary artery at autopsy may be misleading. Functionally, much blood may pass through the involved artery because of the distensibility of the vessel, unless the clot is adherent all around. However, a near-total occlusion of the pulmonary artery may be almost as incompatible with life as total closure. Thus the final episode in a particular patient may be progressive accretion and growth of the clot to complete or nearly complete occlusion. Of course, the slowness of the vessel obliteration is important in the full development of collaterals. Then, a more complete occlusion is better compensated for by development of collaterals and right heart hypertrophy.

Summary

1. A total of 11,511 consecutive autopsies from the Queens Hospital Center, Jamaica, N. Y., was reviewed. This covers a period from late 1935 through 1954. Twenty-one cases of chronic massive pulmonary artery thrombosis were found, an incidence of 0.18%.

2. The age incidence varied from an infant of 15 months to a female of 89 years. Both the mean and median ages were 59 years.

3. Both right and left main pulmonary arteries were involved in eight cases, the right main pulmonary artery in nine, and the left in four.

4. Six of the cases were fairly definitely secondary to previous pulmonary embolization. In the remaining 15 cases we could not be certain, but the probabilities are that several of these were autochthonous.

5. Fifteen of the cases were associated with chronic pulmonary disease.

6. The clinical picture was usually masked by the underlying chronic pulmonary or cardiac disease. However, the outstanding symptom was dyspnea out of proportion to the underlying disease and usually refractory to all treatment. A history or clinical evidence of preceding pulmonary embolization may also be helpful in some instances.

7. When pulmonary thrombosis is suspected, x-ray of the chest, fluoroscopy and angiocardiography may provide additional confirmatory evidence of its presence.

8. The terminal clinical picture in many instances was that of a failing cor pulmonale.

9. As this syndrome receives more recognition, the clinical diagnosis should be made with greater frequency in the future. When diagnosed, a prolonged trial of anticoagulants is justified in view of the usually dire prognosis.

SUMMARIO IN INTERLINGUA

Chronic thrombosis del principal arteria pulmonar o de su dextere o sinistre branca principal es rar, e le casos reportate es pauco numerose.

Esseva examinate le protocollos de 11.511 consecutive autopsias executate al Hospital Central de Queens (un institution municipal a Jamaica in New York City). Isto includeva le periodo ab le fin de 1935 usque al fin de 1954. Esseva trovate 21 casos de massive thrombosis del arteria pulmonar, lo que representa un frequentia de 0,18 pro cento. Le etates del patientes variava inter 15 menses e 89 annos. Le etate median del gruppo e etiam le etate del individuo al centro del gruppo esseva 59 annos.

Ambe principal arterias pulmonar esseva involvite in 8 casos. Solo le principal arteria pulmonar al dextera esseva involvite in 9 casos e illo al sinistra in 4 casos. In 6 del casos il se tractava satis clarmente de un disveloppamento secundari a un previe embolisation pulmonar. In plures inter le remanente 15 casos, le formation del thrombo occurreva probabilemente in le arteria pulmonar sin previe embolisation.

In 15 del casos il habeva un associate chronic morbo pulmonar. In omne casos de thrombosis unilatere combinate con chronic morbo pulmonar, le due entitates esseva al mesme latere.

Le manifestationes clinic del thrombosis esseva generalmente mascate per le subjacente chronic morbo pulmonar o cardiac. In 17 casos le principal symptoma esseva sever dyspnea foras de proportion al subjacente morbo e refractori a omne formas de tractamento.

Un historia de signos clinic de previe embolisation pote esser utile in establir le diagnose. Roentgenogrammas thoracic pote revelar un massa hilar con diminution o absentia de marcas vascular in le campo peripheric del pulmones. Examines fluoroscopic pote demonstrar le absentia de pulsationes hilar al latere afficite. Angiocardiographia pote monstrar un manco de plenation del afficite arteria pulmonar. In studios de cardiocatheterisation le constatationes include un alte pression dexteroventricular con un basse rendimento cardiac.

Le aspecto clinic terminal esseva in multe casos illo de corde pulmonal in stato de disfallimento. In 14 del 21 casos in le presente serie, varie grados de hypertrophia o dilatation dexterocardiac esseva constatate al autopsia.

In tanto que iste syndrome attrahe plus attention, su diagnose per medios clinic deberea devenir plus frequente. Quando le diagnose del syndrome es establite, un prolongate curso de anticoagulantes es justificate in vista del character usualmente pessimista del prognose.

Es presentate 21 casos de chronic massive thrombosis del arteria pulmonar. Le constatationes clinic e autoptic es tabulate, analysate, e discutite. Factores de influentia super le syndrome e su probabile pathogenese es discutite. Un aspecto notabile del studios autoptic esseva le presentia de un previe embolo pulmonar o de thromboembolismo de alicun altere location in 14 casos. In despecto del massive thrombosis, il non habeva massive infarcimento pulmonar, ben que minor infarcimentos esseva notate in alicun casos.

Le litteratura in re iste entitate es revidite in selection, specialmente con referentia a pathologia, physiologia pathologic experimental e studios roentgenographic e clinic.

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THE CLINICAL VALUE OF RENAL BIOPSY * †

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The Kea parrot kills sheep by pecking at their kidneys with its large, hawklike beak.‡ The human counterpart of this bird makes ill-advised stabs with large-bore biopsy needles at the kidneys of patients, and is astounded when he lacerates the organ and endangers the patient's life! Besides laceration of the kidney, other major potential hazards of renal biopsy are retroperitoneal hemorrhage, renal infarct, anuria and dissemination of infection. In the past, biopsy of the kidney was considered too dangerous, but in 1951 Iversen and Brun [1] showed that, in the right hands and with proper care and technic, the procedure is safe. In fact, to date Iversen and his colleagues,[2] Parrish and Howe,[3, 4] Jackson and his associates,[5, 6] and our group have done just under 800 biopsies among us without a death and with little morbidity.

Elsewhere we have described in detail our technic of percutaneous biopsy of the kidney in the prone position.[7, 8] These papers also discussed the indications and contraindications to doing the biopsy. They describe the preoperative and postoperative measures taken to protect the patient, the management of complications, and the methods of handling the tissues and cultures. Modifications necessary in taking biopsies at operations and in pregnant women, or in patients who could not lie prone by reason of disease or infirmity, were also described. It was also established that the small amount of tissue removed gave a representative picture of any diffuse parenchymatous renal disease that might have been present in the organ.[9]

The inherent difficulty with renal biopsy is in finding the organ with the biopsy needle. We use intravenous pyelograms and an atraumatic, fine exploring needle to locate the lower pole of the kidney before we insert the

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‡ The olive green, handsome Kea parrot (*Nestor notabilis*) is confined to the South Island of New Zealand. Originally it fed on carrion, grubs, fruit and seeds, but in 1840 the white settlers introduced sheep and other mammals into New Zealand. It was not long before the Kea, in its search for food, learned to relish the offal around the slaughterhouses of sheep farms. This taste for flesh led it to acquire a macabre and grisly habit. Becoming particularly fond of perirenal fat, it used its large, hawklike beak to obtain this delicacy by pecking its way through the back of living sheep. In doing this it injured the kidneys of the animals, who bled to death. Whether it learned this habit through pecking at ticks or at scabs on the backs of sheep is not known, but the Kea has been hunted remorselessly by the shepherds and is in danger of extinction. (Oliver, W. R. B.: New Zealand birds, Wellington, 1940.)

thin Franklin-Vim-Silverman biopsy needle to secure a small core of renal tissue. In the prone position, a sandbag placed under the abdomen pushes the kidney near the surface of the back, and also insures hemostasis after the biopsy has been taken. The point of the exploring needle is in the kidney when that portion of it outside the skin swings through a wide arc with deep respiration. Exact location of the kidney by this simple maneuver is the reason why this technic is more efficient in obtaining tissue than any other published method.[1, 3, 5, 10, 11, 12, 13, 14, 15, 16]

The main contraindications which we have encountered have been progressive, severe uremia, a hemorrhagic diathesis, lack of coöperation on the part of patients, severe calcific atherosclerosis, and "surgical" lesions of the organ such as hydronephrosis. Table 1 describes an analysis of the first 200 attempts at biopsy. There were no deaths, nor was surgical intervention necessary. Retroperitoneal hemorrhage did not occur, nor did we disseminate infection from an infected organ. The procedure was surprisingly painless except in five patients who had transient renal colic due to the passage of small clots of blood down the ureter. Seven patients

TABLE 1

Analysis of the First 200 Attempts at Renal Biopsy in the Prone Position

1. Tissue obtained	186
2. Transitory renal colic	5
3. Transitory back pain	6
4. Recurrent hematuria	2
5. Transfusion	1
6. Other complications	0

had transient pain in the back after the anesthetic wore off. In two, intermittent hematuria occurred after the biopsy, but needed no special treatment. One patient, an old gentleman with calcific atherosclerosis, bled into his bladder soon after the biopsy and was given a pint of blood. He made an uneventful recovery. Adequate tissue was obtained 186 times (93%).

THE CLINICAL VALUE OF RENAL BIOPSY IN DIAGNOSIS

The difficulties in making an exact diagnosis of renal disease during life have been pointed out by many clinicians, and by Christian [17] in particular. Biopsy of the kidney is more accurate than any other method in making an exact diagnosis. There is no need to labor this point but it must be obvious that, as time goes by, biopsy of the kidney will become more and more valuable as new therapeutic measures are found to combat each of the disease processes which involve the kidney.

Castleman and Smithwick [18] and Heptinstall [19] examined renal biopsy material obtained with a knife during sympathectomy and found they could establish whether there was a primary renal cause for hypertension. Bjørneboe et al.[20] described the value of renal biopsy in the exact diagnosis

of the nephrotic syndrome. Renal biopsy has also been used to diagnose sarcoidosis of the kidney,[16] tuberculosis,[21] capillary glomerulosclerosis [22, 23, 24] and other diseases, such as potassium deficiency nephropathy.[25] We have found it to be of major value in making an exact diagnosis: in the nephrotic syndrome [26] (table 2); in diseases of reaction ("collagen" diseases); [27, 28] in patients suspected of having amyloidosis [29] or pyelonephritis; [5] and in various types of hypertension, when the clinical findings were not helpful. It was also useful in determining the exact lesion of the kidney in pregnant women ill with the syndrome of "toxemia of pregnancy," [30] and in other less common conditions such as secondary hyperparathyroidism [31] and essential hematuria or proteinuria.

Although Cazal [32] has done a few biopsies on patients with renal neoplasm, we believe that the danger of spreading neoplastic cells along the needle track is too real to warrant biopsy in cases suspected of having a tumor of the kidney. This problem should be settled by an exploratory operation.

TABLE 2

Histologic Diagnoses in 40 Adult Patients with the Nephrotic Syndrome

No. of Cases	Diagnoses	No. of Patients Biopsied Serially
14	Glomerulonephritis	4
11	Diabetes 8 with nephrosclerosis 3 with capillary glomerulosclerosis	2
7	Lupus erythematosus disseminatus (3 with pseudonephrotic syndrome)	5
2	Renal vein thrombosis	2
2	Lipoid nephrosis	2
1	Primary renal amyloidosis	1
3	Undiagnosed	

The following case report describes the value of biopsy of the kidney in making an exact diagnosis of the renal lesion in a patient ill with hypertension:

CASE REPORTS

Case 1. A 45 year old executive was known to have had normal blood pressure and urinalysis for many years. On routine examination in December, 1954, the blood pressure was elevated, and red blood cells and protein were found in the urine. Hypertensive retinopathy appeared and progressed rapidly. The clinical diagnosis rested between malignant hypertension and acute glomerulonephritis. Sympathectomy was considered. A renal biopsy showed active chronic pyelonephritis (figure 1). There was an excellent response to therapy with antihypertensive drugs and antibiotics.

A 45 year old sales manager, a patient of Dr. Edwin Irons, was admitted to hospital on January 3, 1955. He had no symptoms at this time. In October, 1954, he had a febrile illness which came on fairly suddenly and lasted six days. He had generalized aches and pains, nausea, occasional vomiting, and abdominal and back pain. He was treated with penicillin and Terramycin. The systolic blood pressure at this time was 140 mm. Hg.

FIG. 1. *Case 1.* Photomicrograph (H. and E., × 225) of renal biopsy. Patient had a blood pressure of 250/150 mm. Hg and papilledema. The glomerular tufts are normal save for minimal congestion. Bowman's capsule is thickened and fibrosed. Note the marked interstitial fibrosis with numerous foci of chronic inflammatory cells. The tubules are atrophic. The small arteries are distinctly thickened and their lumina are narrowed.

There was no history to suggest any renal affection in the past, and there was no family history of hypertension. For 20 years he had seen his physician for yearly physical examinations. His physician had always found normal urine and normal optic fundi, and his blood pressure had ranged at about 150/85 mm. Hg. On December 30, 1954, he again attended for routine examination. This time the blood pressure was elevated to 180/110 mm. Hg; there were changes in the eyegrounds (Keith-Wagener grade II), and urinalysis showed protein 2 plus and many red blood cells. A few white cells and granular casts were found.

On admission the patient was an apprehensive, well built man who appeared neither acutely nor chronically ill. The pulse rate was 90 per minute and the blood pressure 220/130 mm. Hg. The heart was normal in size, and the sounds were natural. Arteriolar narrowing, "copper wiring," and marked nicking of veins by arterioles at the A-V crossings were noted in the optic fundi. Neither exudates nor hemorrhages were seen. The remainder of the physical examination was within normal limits.

The specific gravity of the urine was 1.011; little protein (0 to 1 plus, and a 24 hour protein excretion of 0.3 gm.) was found. There were 2 leukocytes per high power field. Numerous bacteria were seen, but culture of the urine was sterile. Thirty per cent of 6 mg. phenolsulfonphthalein (P.S.P.) injected intravenously was excreted in 15 minutes. The urea clearance was 65% and 45% of average normal renal function in the first and second hours. Normal sized kidneys were noted on an intravenous pyelogram, with good excretion of dye. The patient was able to concentrate his urine to a specific gravity of 1.011. The blood urea nitrogen was 15 mg./100 ml., and nonprotein nitrogen was 39 mg./100 ml. The hematocrit was 45%, and the leukocyte count was 7,700/mm^3. X-ray of the chest was normal, and the electrocardiogram suggested mild left ventricular hypertrophy.

By January 11 there were a few flame-shaped hemorrhages in the optic fundi, and the patient complained of progressive blurring of vision. Four days later, multiple flame-shaped hemorrhages and cotton-wool exudates were seen, and there was early papilledema (K-W grade IV). The blood pressure was 220/120 mm. Hg. By this time the urine had been examined on many occasions, but no abnormality was found save that a trace of protein was seen on two or three occasions.

The clinical diagnosis rested between malignant hypertension and acute glomerulonephritis. His case was discussed at "Grand Rounds." At that time sympathectomy was suggested as the method of treatment because of the rapid progression of the findings in the eyegrounds.

Renal Biopsy (*figure 1*): On January 19 renal biopsy was done. The sections contained adequate cortex (13 glomeruli), with a small fragment of medulla. The glomerular tufts were normal. No basement membrane thickening was seen. The capillaries contained a normal number of red blood cells. There was severe diffuse interstitial fibrosis. In many places this extended into and involved Bowman's capsule, which was distinctly thickened in many of the glomeruli. A diffuse infiltration of chronic inflammatory cells was seen in the interstitial tissue, which was not edematous. Most of the tubules were atrophic, and their lumina were markedly narrowed. They contained neither casts nor inflammatory cells. The small arteries and arterioles were thickened, and in many areas their walls were hyalinized. However, no evidence of necrosis of the arteriolar walls was seen. Culture of the renal biopsy tissue was sterile.

Microscopic Diagnosis: Active chronic pyelonephritis.

Following the biopsy the patient was treated with Serpasil and Ansolysen. When the results of the biopsy became known he was given a 14 day course of treatment with tetracycline, 1 gm. daily.

When last seen (on March 24), the patient was receiving Ansolysen, 80 mg., and Serpasil, 25 mg. four times daily. His blood pressure was 155/85 mm. Hg. No

thickened and fibrosed. Note the marked interstitial fibrosis with numerous foci of chronic inflammatory cells. The tubules are atrophic. The small arteries are distinctly thickened and their lumina are narrowed.

new lesions had appeared in the optic fundi; the old lesions had decreased in size, and there was no papilledema; his vision had improved. Urinalysis showed no abnormality. The heart was normal, and chest x-ray and electrocardiogram were normal.

Comment

Despite the fact that Longcope [33] and Weiss and Parker [34] have pointed out in their classic papers that pyelonephritis is a common cause of malignant hypertension, we are prone to forget this. The diagnosis of pyelonephritis was not mentioned at "Grand Rounds" and was not considered

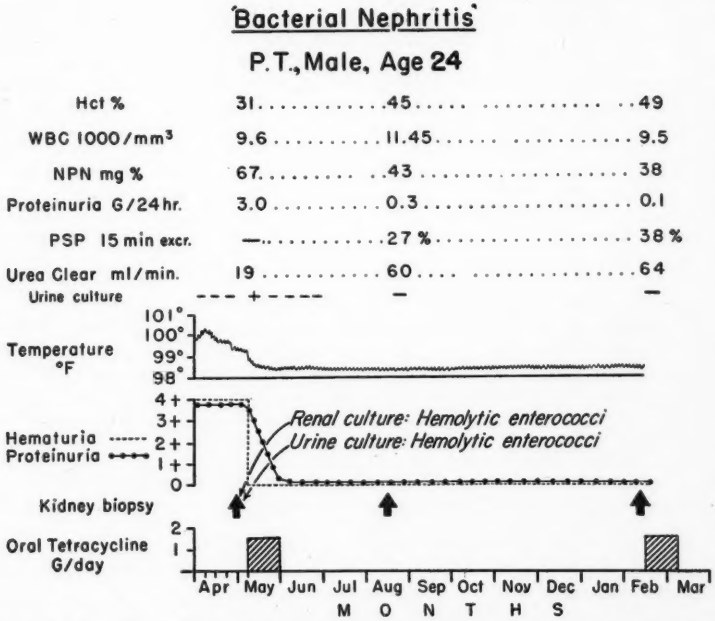

FIG. 2. This chart illustrates the clinical course of case 2, ill with "bacterial nephritis" due to hemolytic enterococci. Note the response to therapy with tetracycline.

likely by any of the physicians who saw the patient. Avendaño et al.[35] have noted pyelonephritis in 40% of patients with hypertension, and claim to have cured 10 out of 18 patients with antibiotics alone. The value of renal biopsy in this case speaks for itself. Although this patient had a shower of red blood cells in the urine on one occasion, it was essentially normal thereafter. This hemorrhage, which suggested acute glomerulonephritis, is seen occasionally in pyelonephritis, but many patients with this disease go along for years without protein or other abnormalities in the urine and with a urinary sediment which is perfectly normal.

The rather severe interstitial inflammation and fibrosis and the involvement of Bowman's capsule by fibrous tissue were strong evidence that the kidneys were damaged by the pyelonephritic process. The absence of glomerular changes added strength to this interpretation. The severe arteriolar sclerosis was considered to be part of the chronic pyelonephritic process.

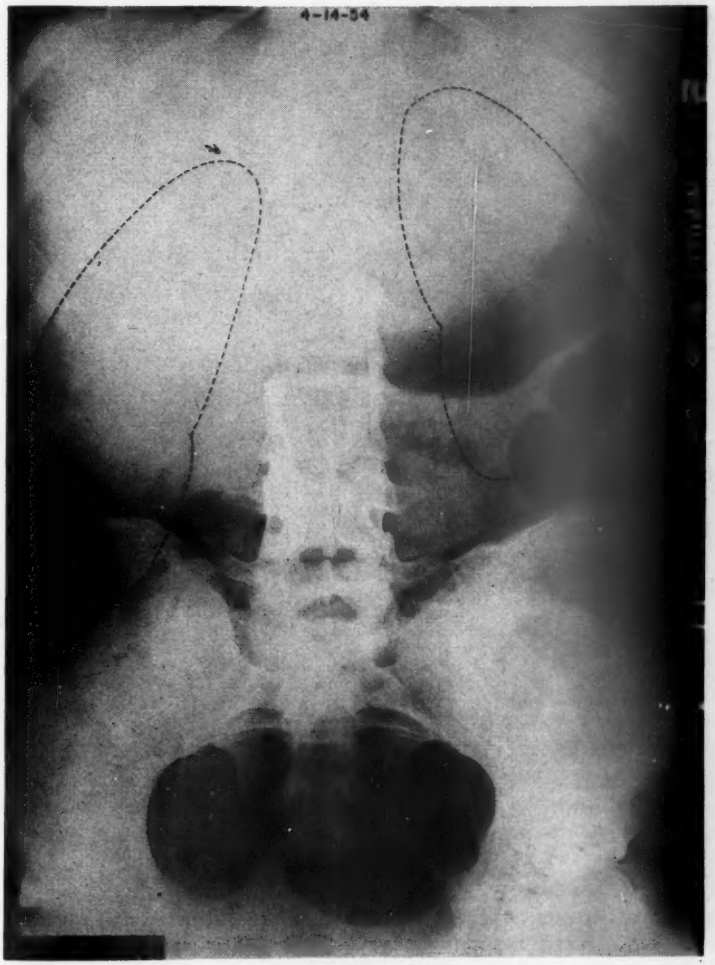

FIG. 3A. *Case 2.* X-ray of the abdomen illustrating, on April 14, the bilateral kidney enlargement before therapy with tetracycline.

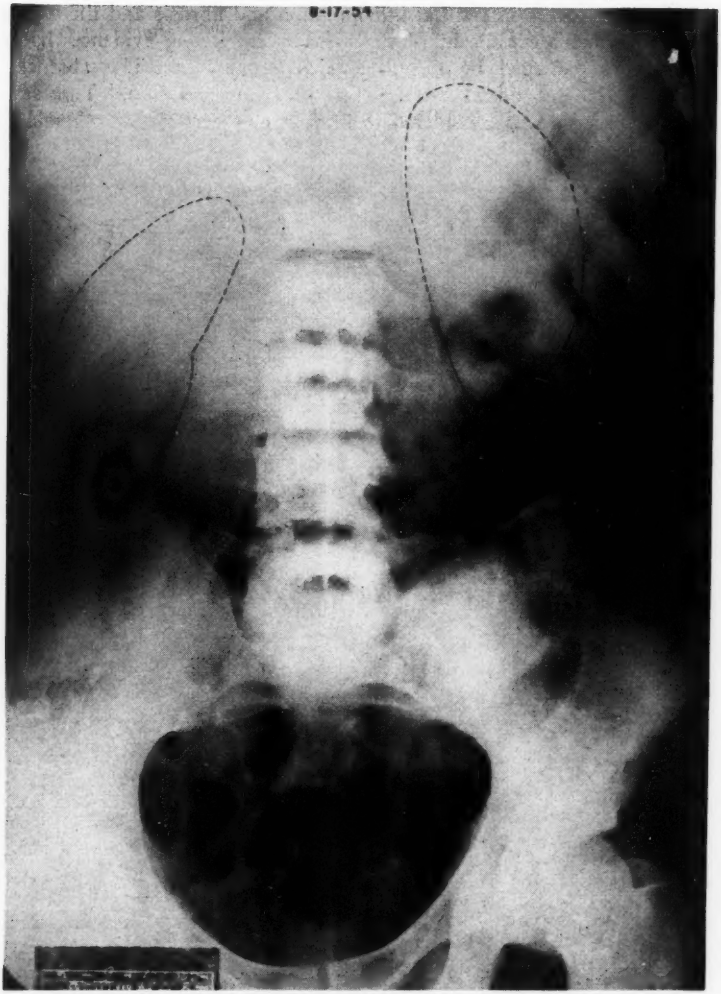

FIG. 3B. Four months later: restoration of the kidneys to normal size.

THE CLINICAL VALUE OF RENAL BIOPSY IN TREATMENT

Rational treatment follows logically on exact diagnosis, and each biopsy of the kidney which has been examined has affected the management of our patients. Minor changes in histology have spurred us on to the vigorous use of therapeutic procedures in the hope of a cure, and major damage to the kidney has made us cautious, lest we irreparably harm the organ and

the patient. Brun [36] has used renal biopsy to select anuric patients for dialysis on the artificial kidney. He found that those patients who had acute lesions of the kidney responded best. Bjørneboe and his associates [37] have used renal biopsy to select patients with the nephrotic syndrome for therapy with ACTH. They found that a diuretic response to hormone therapy appeared only in patients with minimal histologic evidence of glomerular damage.

Renal biopsy seems to be a more accurate method than cultures of the urine in determining exactly the organism responsible for infection within the kidney.[5, 38] As we shall show below, occult infection of the kidney can be discovered at present only by renal biopsy.

Case 2. A 24 year old factory worker complained of fatigue and gross hematuria (figure 2). He had been in poor health for two years. He complained of his joints, of loss of weight, transient edema, thirst, polyuria and nocturia. He was anemic; there was a hemic murmur, and the spleen and kidneys were enlarged. He ran a low fever. The urine was loaded with red blood cells and protein. Seventeen blood cultures, one bone marrow culture and 10 urine cultures were sterile. The clinical diagnosis was subacute bacterial endocarditis or chronic glomerulonephritis. An unusual lesion was found by renal biopsy (figure 4 and table 4), and a pure culture of hemolytic enterococcus was grown from the renal tissue. The identical organism appeared in the urine soon after the biopsy, but later cultures were sterile. The organism was sensitive to tetracycline, which was administered for two weeks. This restored him to full health (figure 3 and table 3).

TABLE 3

Discrete Renal Function Tests in Case 2, Ill with "Bacterial Nephritis," before and after Treatment with Tetracycline

Discrete Renal Function Tests	Before Therapy	After Therapy
Glomerular filtration rate (C_{inulin}), ml./min.	30	94
Renal plasma flow (C_{PAH}), ml./min.	330	430
Tubular mass (T_{MPAH}), mg./min.	23	54
Filtration fraction	0.09	0.22

A 24 year old, poorly developed, saturnine, lean Italian laborer was admitted on April 5, 1954, complaining of fatigue and "whiskey-colored" urine.

At the age of six he was told he had "leakage of the heart." In the spring of 1950 he had a painful swelling of the left ankle. Four months later the right ankle became painful. In April, 1953, progressive fatigue forced him to give up his work. A year later he developed arthralgia, orthopnea, anorexia, polyuria, nocturia and hematuria.

In March, 1954, he received penicillin for a lymphangitis of the calf. Three days later he noticed hematuria and was treated in hospital for two weeks, where he was given a course of antibiotics. There was no improvement, and subsequently he had another attack of arthralgia. Toward the end of March he noticed transitory swelling of his trunk and face. He was feverish, and his urinary symptoms worsened.

Physical Examination: The patient was a pale, acutely ill, poorly developed male with shrunken eyes and prominent clavicles. There was no peripheral edema. The rectal temperature was 101.8° F. The pulse rate was 96 and regular. The blood pressure was 152/86 mm. Hg. He weighed 112 pounds. A few petechiae were seen in one popliteal fossa. There was generalized lymphadenopathy. Examination of the fundi was normal. The lungs were clear. The heart was enlarged to left.

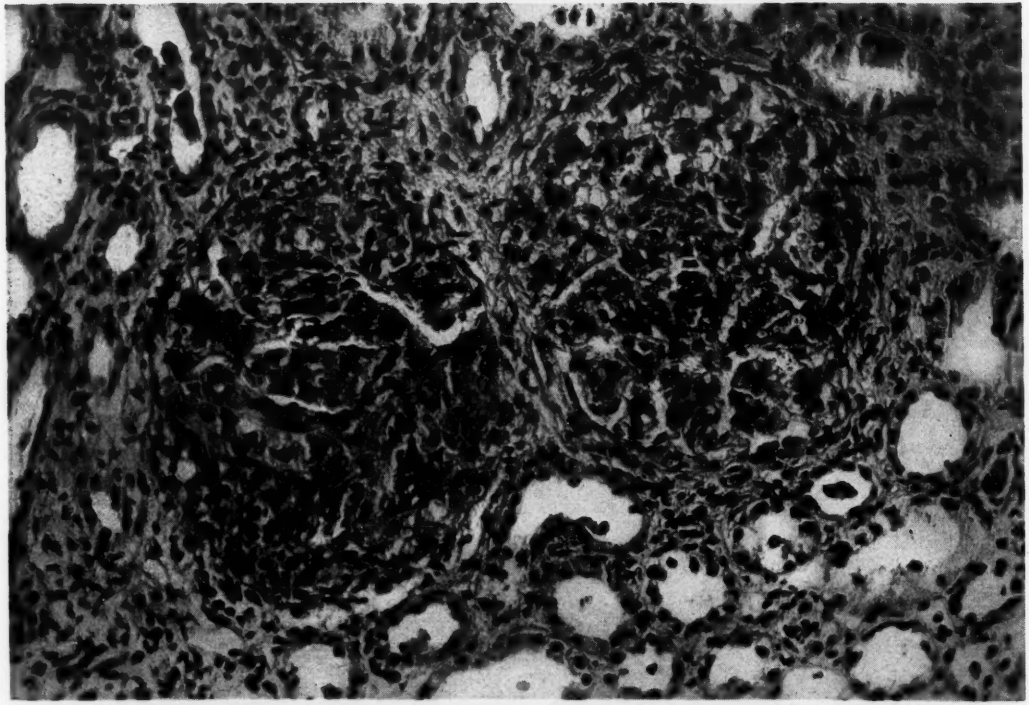

FIG. 4. *Case 2.* Photomicrographs (H. and E., ×225) of renal biopsies of case 2, ill with "bacterial nephritis."

A. First renal biopsy. Hemolytic enterococci were grown from the biopsy culture. Note the marked hypercellularity and ischemia of the glomeruli, which are compressed by large epithelial crescents. The interstitial tissue is edematous and contains foci of chronic inflammatory cells.

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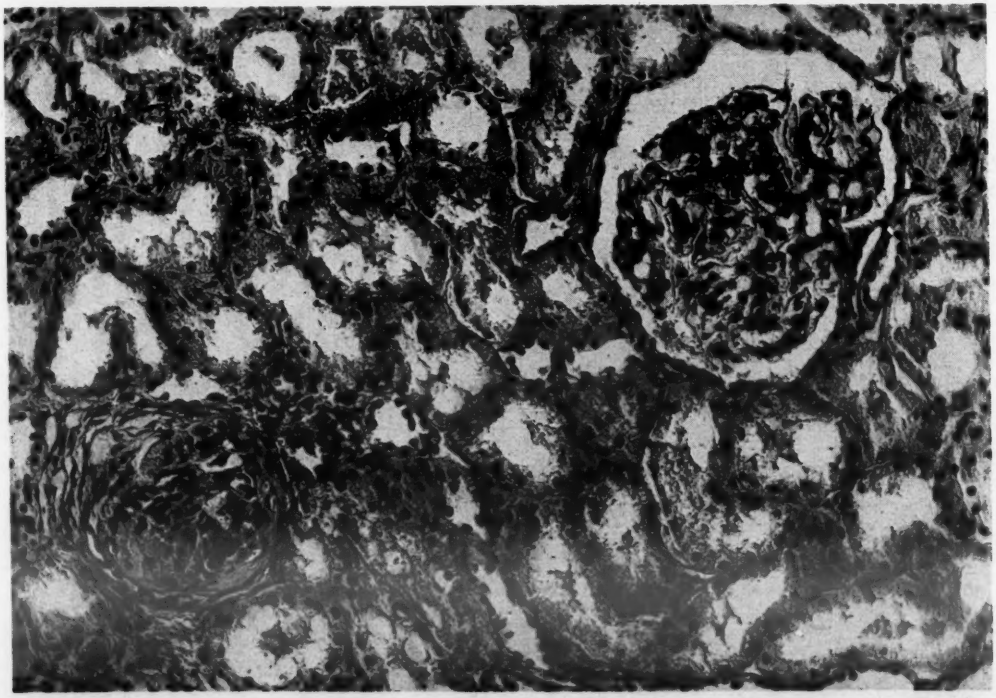

FIG. 4B. Second renal biopsy, taken four months after tetracycline therapy. Note the hyalinized glomerulus and the normal appearing glomerulus.

A harsh grade III systolic murmur was heard over the pulmonic area. The second aortic sound was louder than the second pulmonic sound. The spleen was palpated 4 cm. below the left costal margin. The edge was smooth, soft and nontender. The liver was not felt. Both kidneys were enlarged but were not tender. There was painful and limited motion of the left elbow.

Laboratory Data: On his admission the specific gravity of the urine was 1.011; the pH was 6.5, and there was 4 plus proteinuria (30 gm. per 24 hours). Examination of the centrifuged urine revealed many erythrocytes, 5 to 7 leukocytes, and many hyaline and granular casts per high power field. The hemoglobin was 8.5 gm./100 ml.; the hematocrit was 30%; the leukocyte count was 9,550/mm^3, with a differential count of 84% neutrophils, 14% lymphocytes and 2% monocytes; the erythrocyte sedimentation rate was 28 mm./hour. The blood nonprotein nitrogen was 67 mg./100 ml.; the blood creatinine was 2.5 mg./100 ml. Studies of the serum showed: albumin, 3.7 gm./100 ml.; globulin, 2.9 gm./100 ml.; cholesterol, 213 mg./100 ml.; CO_2 combining power, 23 mM/L.; chlorides, 110 mEq./L.; potassium, 3.4 mEq./L.; sodium, 143 mEq./L.; calcium, 8.6 mg./100 ml.; bilirubin, 0.16 mg./100 ml.; thymol turbidity, 8.9 units; 48 hour cephalin flocculation test, 2 plus. The prothrombin time was slightly prolonged (to 15.8 seconds). The antistreptolysin "O" titer was 166 units. Hypercellularity of the granulocytic elements was found on examination of the bone marrow. Hargraves' ("L.E.") cells were not found on a special preparation of the bone marrow. Cultures of the urine (10), blood (17), and bone marrow were sterile. On x-ray examination there were moderate enlargement of the left ventricle, uniform enlargement of both kidneys with a poor excretion of Diodrast (figure 3), and normal hands and feet.

TABLE 4

Analysis of Histologic Findings in the Tissue of 3 Serial Biopsies of the Kidney from Case 2, Ill with "Bacterial Nephritis," before Treatment with Tetracycline (April 27, 1954*) and after Treatment (August 17, 1954† and February 17, 1955‡)

	First Biopsy*	Second Biopsy†	Third Biopsy‡
Glomeruli	Crescent formation (10) Marked cellular infiltrate (10) Mild changes (2) (22)	Completely hyalinized (5) Mild cellularity (15) Almost normal (17) (37)	Completely hyalinized (4) Minimal cellularity (6) Essentially normal (12) (22)
Interstitial tissue	Acute and chronic inflammatory cells Periglomerular cellular infiltrate Severe interstitial edema	Foci of chronic inflammatory cells around hyalinized glomeruli No interstitial edema	Foci of chronic inflammatory cells around hyalinized glomeruli No interstitial edema
Tubules	Epithelial degeneration Many RBC casts and free RBC's in tubules	Normal Few hyaline and pigment casts	Normal No casts
Vessels	Normal	Normal	Normal
Culture	Hemolytic enterococci	Sterile	Sterile

Renal Function: Results of tests of discrete renal function were as follows: The glomerular filtration rate (C_I) was 30 ml./min.; the effective renal plasma flow (C_{PAH}) was 330 ml./min.; the tubular mass (T_{MPAH}) was 23 mg./min.; the filtration fraction was 0.09. The creatinine clearance was 39 ml./min. The urea clearance was 19 ml./min. (table 3*).

The urinary findings and low grade fever persisted. The diagnosis rested

*We are indebted to Dr. James A. Schoenberger, who performed the tests of discrete renal function.

between pulmonary stenosis with subacute bacterial endocarditis and subacute glomerulonephritis with anemia and a hemic murmur. On April 22 a right renal biopsy was done.

Renal Biopsy (figure 4a and table 4): The sections contained adequate cortex (22 glomeruli), but little medulla. All glomeruli were abnormal; diffuse or focal hypercellularity of the tuft was noted in many. In addition, lobulation of the tufts and epithelial crescents of Bowman's capsule were present in most of the glomeruli. Some of the crescents were replaced by fibrous tissue proliferation. In a few glomeruli, eosinophilic, smudgy material and inflammatory cells were noted. The interstitial connective tissue was moderately edematous and increased in amount, especially around the more severely damaged glomeruli. In these areas there was considerable active infiltration by chronic inflammatory cells and by a few polymorphonuclear cells. The majority of the tubules were altered. A large proportion were small; in others, degeneration of the tubular epithelium was noted. Red blood cell casts or free red blood cells were seen in many. An occasional hyaline cast was also seen. The blood vessels were not remarkable.

Microscopic Diagnosis: Subacute glomerulonephritis.

Culture of Renal Biopsy: A pure growth of hemolytic enterococcus was obtained from the culture of a small piece of renal tissue. The identical organism was found in cultures of urine taken on the day of biopsy, but later cultures were sterile. The organism was sensitive to tetracycline.

Results of Treatment: The patient was given a course of tetracycline, 2 gm. by mouth daily for 14 days. Two days after starting therapy he became afebrile, the hematuria disappeared, urinary symptoms abated, and proteinuria decreased markedly. Ten days after treatment the creatinine had fallen to 1.4 mg./100 ml. and the nonprotein nitrogen to 38 mg./100 ml. Two weeks later they had dropped to 1.0 and 25 mg./100 ml., respectively. He was discharged a week later, on June 14, much improved.

Second admission—August, 1954: On August 16 he was re-admitted to hospital. He felt very well and firmly believed he was restored to his previous state of health. Physical examination revealed the blood pressure to be 118/68 mm. Hg. The fever, pallor, splenomegaly, cardiomegaly and cardiac murmur noted on previous examination had disappeared.

The urine was clear (0.3 gm. protein in 24 hours). On examination of the centrifuged urine 5 to 8 erythrocytes, a few leukocytes and an occasional granular cast were seen. The hematocrit had risen to 44%. The blood nonprotein nitrogen was 38 mg./100 ml. The serum albumin was 4.9, and the globulin was 2.3 gm./100 ml. Tests of discrete renal function were normal (table 3). The heart and kidneys were of normal size on x-ray (figure 3). Cultures of the urine and blood were sterile. A second renal biopsy was done. Cultures of the renal tissue were also sterile. The patient was discharged on August 18, 1954.

Second Renal Biopsy (figure 4b and table 4): The sections contained adequate cortex (37 glomeruli) and a small portion of medulla. Most glomeruli were essentially normal except for slight focal hypercellularity due to endothelial cell proliferation. The capillary tufts were distended and filled with blood, and abundant proteinaceous material was noted in Bowman's space. Fairly advanced hyalinization of the tuft was seen in five glomeruli, which were reduced in size. There were minimal interstitial edema and fibrosis. Around the hyalinized glomeruli, however, there was distinct fibrosis, with infiltration of chronic inflammatory cells. In these areas the tubules were atrophic, but elsewhere they appeared essentially normal. Some contained proteinaceous material or hyaline casts. An occasional tubule contained an orange-green cast, perhaps of hemoglobin origin. The blood vesels were normal.

Microscopic Diagnosis: Chronic focal glomerulonephritis.

Third Admission—February, 1955: The patient had no complaints and was in excellent health. He had gained 10 pounds in weight. Physical examination was normal. A third renal biopsy was done. Cultures of blood, urine and renal tissues were sterile. The hematocrit was 49%. On examination of the urine the specific gravity was 1.028; a trace of protein was found; on microscopic examination 5 to 8 erythrocytes, 3 to 4 leukocytes and occasional casts were seen. The phenolsulfonphthalein excretion was 38% in 15 minutes, and the urea clearance was 64 ml./min. A prophylactic course of tetracycline was given.

Third Renal Biopsy (table 4): Adequate cortex (22 glomeruli) and medulla were noted in the sections. Most of the glomeruli were entirely normal. Three contained small foci of hypercellularity, four were completely hyalinized, and three glomeruli were quite cellular and ischemic, and contained eosinophilic areas suggestive of past necrotizing changes. There was some infiltration of chronic inflammatory cells in these three glomeruli. Elsewhere the interstitial connective tissue was normal, with slight fibrosis around the hyalinized glomeruli. The tubules were essentially normal and did not contain casts. The vessels were normal.

Comment

Although the response to therapy was dramatic, the disease process within the kidney was not the result of the type of glomerulonephritis seen in association with subacute bacterial endocarditis. From a clinical point of view Libman's sterile stage of subacute bacterial endocarditis [39] was a likely diagnosis except for the fact that the heart was found to be completely normal after the infection had abated.

The marked periglomerular interstitial inflammation and the focal necrotic features observed in most of the glomeruli were strongly suggestive of an active reaction on the part of the kidney, possibly due to local bacterial action. The sharp decrease in the size of the kidneys following treatment and the disappearance of interstitial inflammation and edema indicated an organ response to antibiotic therapy. This was also reflected in the restoration of renal function to normal. The biopsy taken nine months after therapy revealed a completely normal kidney except for remnants of chronic focal glomerulonephritis which were in an inactive stage. Adequate treatment of this patient depended upon the finding of an organism obtained by culture of kidney tissue. This organism was not found in the bone marrow, in the blood or in the urine. Trauma to the kidney by the biopsy needle allowed it to pass into the urine for a short while.

This unusual situation—positive cultures from the kidney with repeated negative urine cultures—has occurred five times in our first 200 biopsies, and on each occasion the organism which was cultured was eradicated by appropriate antibiotic therapy. This restored abnormal urine findings to normal. These cases do not present the pictures seen in pyelonephritis, from either a clinical or a biopsy point of view.[5, 6] They are a group of infections which are neither purulent nor innocuous. They do not involve perinephric tissues or the pelvis of the kidney. A suitable name for the disease is "sub-

acute bacterial nephritis." At present this condition cannot be recognized except by renal biopsy.[38]

Prognostic Value of Renal Biopsy

Prognosis is an art to which all are called, but in which few excel. Like all judgments in medicine, prognosis is based on data collected both consciously and unconsciously. The tissue obtained so consciously and deliberately by renal biopsy provides, in our experience, the most significant evidence on which to forecast the course of a disease involving the kidney. It has been striking indeed to learn the extent of damage in the kidneys of patients who looked well and in whom laboratory findings were not too severely altered. Renal biopsies have been valuable in making a prognosis, especially in the nephrotic syndrome,[26] in hypertension,[18, 19] in pyelonephritis,[5] in lupus erythematosus disseminatus,[27, 28] in the toxemia-of-pregnancy syndrome,[20] and in diabetes.[22, 23, 24]

The two cases recorded below are of patients who had the nephrotic syndrome. One was a taxi driver, aged 44; the other, a grandmother, aged 65. In both, the laboratory findings were abnormal to approximately the same degree. Both looked equally bloated with edema; neither looked critically ill. In one, renal biopsy disclosed severe glomerular changes, and the prognosis was considered to be poor. In the other the renal biopsy indicated normal glomerular status and marked tubular changes. In her, the prognosis was considered to be good. Time may bear these forecasts out. Our grandmother is now comparatively well, and the taxicab driver is running a steady downward course. These two cases are described below:

Case 3. A taxi driver with nephrotic syndrome. Biopsy showed membranous glomerulonephritis (figure 5a).

A 44 year old, plethoric, stocky taxi driver, a patient of Dr. Gunther, was admitted complaining of edema. This had started in December, 1953, and by January, 1954, had involved the legs, thighs, sacral region and face. At that time he had gross proteinuria, low serum albumin and high serum cholesterol. He was diagnosed as having the nephrotic syndrome due to subacute glomerulonephritis, and did not respond to treatment with cortisone and a diet low in salt. There was no past history of renal disease. The essential findings on physical examination were: edematous upper eyelids, pitting edema of the legs up to the thighs, a blood pressure of 140/86 mm. Hg, and normal funduscopic examination. Examination of the urine revealed gross proteinuria (5.5 gm. per 24 hours). Many granular, hyaline, fatty and cellular casts were seen on microscopic examination. Urine cultures were sterile.

The essential biochemical findings in the blood were: creatinine, 4.1 mg./100 ml., and nonprotein nitrogen, 52 mg./100 ml.; and in the serum, albumin, 2.4 gm./100 ml., and cholesterol, 598 mg./100 ml. The phenolsulfonphthalein excretion was 20% in 15 minutes. Biopsy of the right kidney in June, 1954, showed subacute glomerulonephritis of the membranous type (Ellis type II) (figure 5a).

Since this time the patient has been treated with a low salt diet, intravenous human serum albumin and ACTH. Further biopsy studies revealed progression of the disease, with severe interstitial fibrosis, tubular atrophy and early contraction of the kidney. The histologic diagnosis was chronic membranous glomerulonephritis.

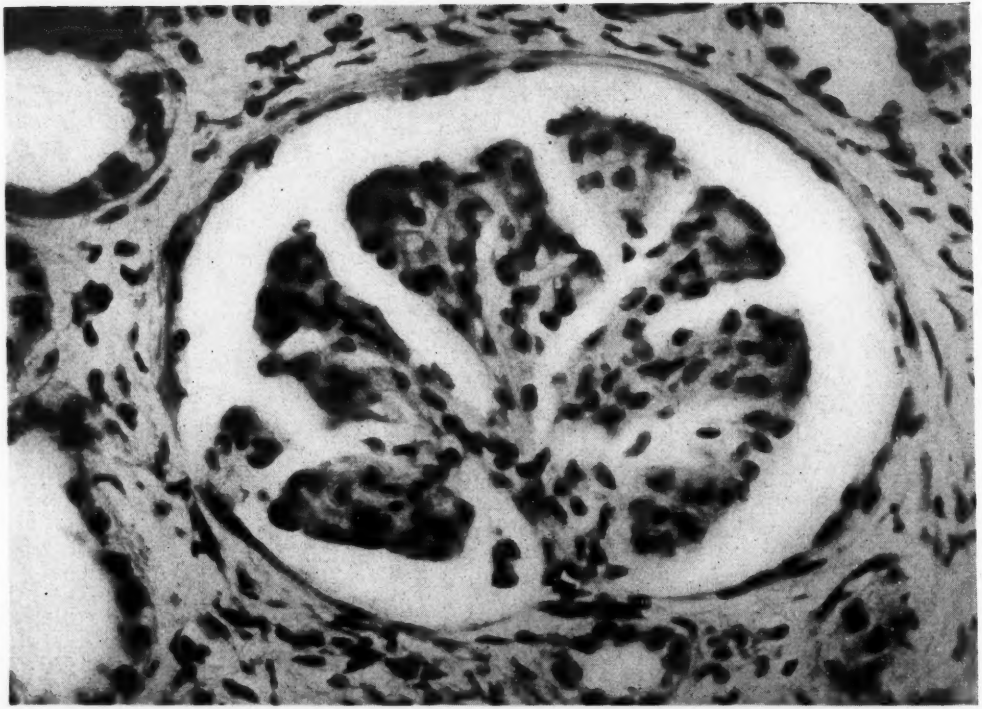

FIG. 5. Photomicrographs (H. and E., × 600) of the renal biopsies of two patients with the nephrotic syndrome. In each, edema first appeared in December, 1953.

A. First biopsy of case 3, taken in June, 1954. Note digitation and ischemia of the glomerular tuft, and the moderate interstitial edema and fibrosis. The diagnosis was membranous glomerulonephritis (Ellis type II).

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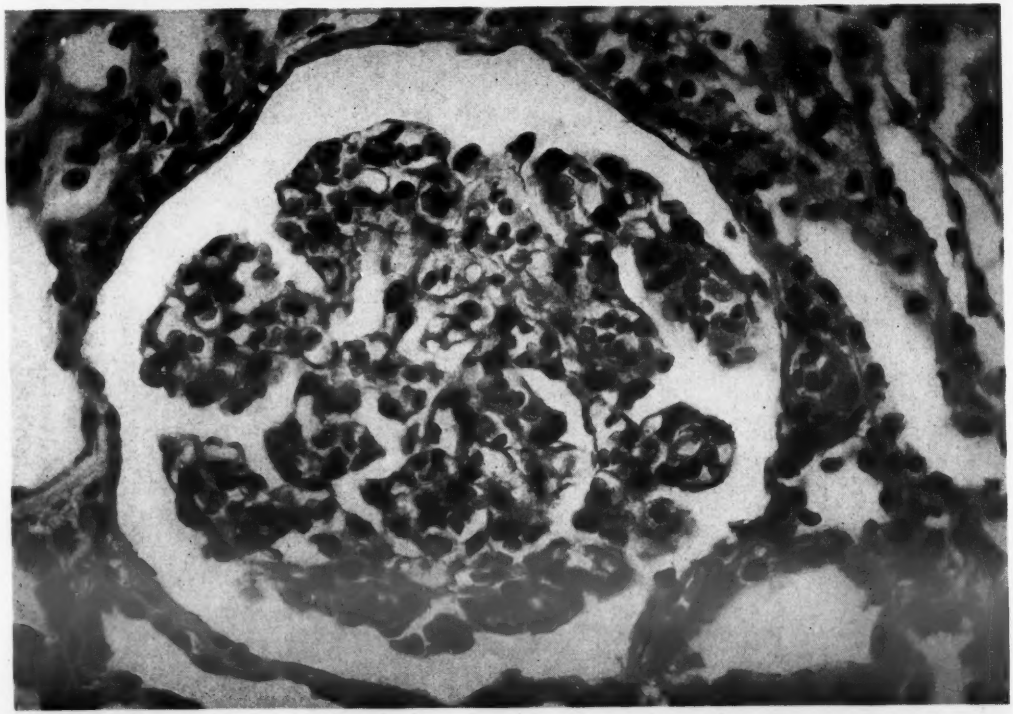

FIG. 5B. First biopsy of case 4, taken in March, 1954. Note the congestion of the glomeruli and peritubular capillaries. The glomerular basement membrane is not thickened. The diagnosis was tubular disease of undetermined type, possibly lipoid nephrosis.

The most recent biochemical data were: in the blood, creatinine, 2.9 mg./100 ml., and nonprotein nitrogen, 55 mg./100 ml.; and in the serum, albumin, 3.5 gm./100 ml., and cholesterol, 515 mg./100 ml. The phenolsulfonphthalein excretion was 11%. At present he is complaining of malaise, nocturia and slight edema.

Case 4. A grandmother with nephrotic syndrome. Biopsy showed tubular changes (figure 5b).

A silver-haired, poorly nourished 65 year old housewife, a patient of Dr. Bianco, was admitted complaining of ankle edema. Two weeks later she was found to have gross proteinuria, low serum albumin and high serum cholesterol. There was no past history of renal disease. The essential findings on physical examination were: pitting edema of legs, thighs and lower abdomen, and periorbital edema. There were small bilateral pleural effusions and minimal ascites. The tongue was beefy and raw, and there were active cheilosis and perlèche. Ophthalmoscopic examination revealed arteriosclerotic retinopathy (Grade II—K-W). On examination of the urine there were gross proteinuria (2.5 gm. per 24 hours), many casts and doubly refractile bodies. Laboratory findings were: blood creatinine, 2.6 mg./100 ml.; nonprotein nitrogen, 31 mg./100 ml.; serum albumin, 1.6 gm./100 ml., and serum cholesterol, 1,400 mg./100 ml. The phenolsulfonphthalein excretion was 0% in 15 minutes, but this may have been the result of a technical error.

Although at first most observers felt that this patient was a case of glomerulonephritis, some later suggested that the disease was the result of malnutrition or a renal vein thrombosis. X-ray studies did not corroborate the latter diagnosis. Renal biopsy findings in March and July were similar (figure 5b). There was severe tubular disease characterized by fatty degeneration and dilatation of the tubules, associated with interstitial edema. The complete lack of any glomerular changes was remarkable. These findings were incompatible with a diagnosis of membranous glomerulonephritis.

The patient was treated with a nutritious diet, high in protein and calories and low in salt. She has made steady progress. When examined in March, 1955, her edema had disappeared, her tongue and mouth were natural, and her general nutrition and health were excellent. Her urine contained a rare cast and protein (3.1 gm. per 24 hours). The blood creatinine was 1.4 mg./100 ml.; the nonprotein nitrogen was 44 mg./100 ml.; the serum albumin was 4.3 gm./100 ml., and the serum cholesterol was 410 mg./100 ml. The phenolsulfonphthalein excretion was 16%.

Renal biopsy was repeated at this time. A patchy, irregular thickening of the glomerular basement membrane was seen, but otherwise the glomeruli were normal. Neither epithelial crescents nor adhesions were seen. Bowman's capsule was normal. In some tubules there were moderate degenerative changes in the epithelium. The interstitial connective tissue in many areas was moderately increased but did not appear edematous.

Comment

When these two patients were first admitted to hospital, most observers thought that their deranged metabolism and severe nephrotic edema were due to glomerulonephritis, although there was no previous history of renal disease. When the biopsies had been done the question of lipoid nephrosis, malnutrition and renal vein thrombosis was raised in case 4 because her glomeruli were normal. It was obvious when the two biopsies were compared that the membranous glomerulonephritis seen in case 3 would progress, and it was felt that the tubular disease seen in case 4 would repair itself if she ate a diet high in protein and calories. Up to now, these prog-

nostications have been justified. The taxi driver's kidneys are shrinking, and his clinical status and laboratory findings mirror the natural history of membranous glomerulonephritis (Ellis type II). Although case 4 is comparatively well, and although the tests of renal function have improved, it is difficult to know what the future course will be. The tubular lesions are much improved, but the glomeruli are now involved, with patchy thickening of basement membrane. We cannot classify the renal disease at present. Lipoid nephrosis and early membranous glomerulonephritis are possibilities, as is a primary nutritional disorder. It is interesting to observe that, although the laboratory findings were similarly deranged, the damage involved the tubules in case 4 and the whole nephron in case 3.

When one attempts to forecast the life span or course of patients ill with the nephrotic syndrome on the basis of renal biopsy findings, it would seem that the worse the glomerulus the worse the prognosis. Inflammatory changes in the interstitial tissue, whether they be due to secondary infection or the result of the primary disease, are a bad prognostic finding.

Serial Renal Biopsy and the Natural History of Diseases

Serial renal biopsy is an ideal method for sampling renal tissue during the progress of disease involving the kidney. In addition to changes in the nephron, changes occurring in the blood vessels or the ground substance are readily observed—better, perhaps, than anywhere else in the body. Therefore, vascular diseases, such as hypertension or periarteritis nodosa, and diseases of reaction, such as thrombotic thrombocytopenic purpura or lupus erythematosus disseminatus (L. E. D.), can be followed.

The correlation of clinical data with progressive histologic changes may provide a basis for more exact clinical diagnosis in the future. A knowledge of the natural history of disease is desirable when powerful hormones or drugs are employed empirically in the treatment of patients. Obviously one would like to know not only if a certain therapy was useful, but also whether one was harming the patient by exhibiting the hormone or drug. The evaluation of such therapy can most properly be made by knowledge of the clinical and pathologic course of the disease.

An empiric therapeutic procedure which is widely employed today is the prescription of steroids for patients with lupus erythematosus disseminatus (L.E.D.). While many claim that this is beneficial, there has been a growing suspicion that this may adversely affect the course of the disease when the kidney is involved.[40] Because of this, we have embarked on a study of the natural history of the renal involvement in L.E.D. by correlating serial renal biopsies with clinical and laboratory observations on patients, some of whom have not received therapy with steroids.[28] The following is a study on such a patient:

Case 5. A 33 year old housewife developed Raynaud's phenomenon (figure 6). Five years later, in December, 1953, a face rash appeared. Nephrotic syndrome with

persistent hematuria was observed in March, 1954. The illness ran a fluctuating course. During this illness marked lethargy, anemia, pleurisy, alopecia, arthralgia and an enlarged liver and spleen were noted. Renal function decreased during the period of observation. The first two renal biopsies revealed subacute glomerulonephritis, and chronic glomerulonephritis was found when the third biopsy was done in February, 1955 (figure 7).

A pleasant and intelligent 33 year old housewife was admitted to hospital on July 7, 1954. For five years she had had attacks of Raynaud's phenomenon. In December, 1953, she developed a rash on the face, neck and extensor aspects of the forearm. At the beginning of January, 1954, she had a severe sore throat with enlarged cervical lymph nodes. Six weeks later she developed pain and swelling of the left ankle; shortly thereafter, swelling of the other ankle, the face and hands occurred.

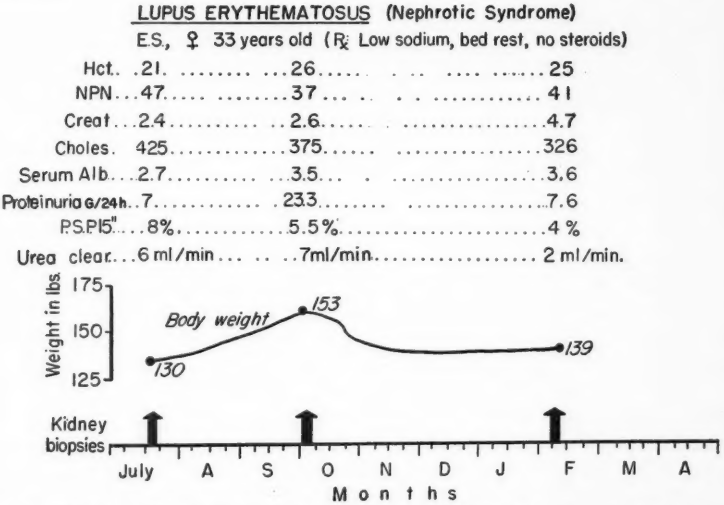

FIG. 6. This chart illustrates the clinical course of case 5, ill with the nephrotic syndrome due to systemic lupus erythematosus.

She was admitted to hospital elsewhere in March. She had a low grade fever and pleuritic pain. Protein was found in the urine, which appeared bloody. She was treated with penicillin, Aureomycin and serum albumin. When she went home on April 16 the swelling had disappeared, but proteinuria and hematuria persisted.

On admission on July 7 she was rather pale. The pulse was 72 per minute and the blood pressure 124/86 mm. Hg. There was a small, atrophic patch of skin on the left cheek. A few small shotty lymph nodes were found, but no other abnormality was detected.

The urine was red. The specific gravity varied between 1.005 and 1.017. A 24 hour specimen of urine contained 9 gm. protein and 20 erythrocytes and 5 to 10 leukocytes, and numerous granular hyaline and broad casts were seen in the urinary sediment.

The total serum protein was 4.9 gm./100 ml. (albumin, 2.2 gm.; globulin, 2.7 gm./100 ml.); the serum cholesterol was 421 mg./100 ml.; the blood creatinine was

FIG. 7. *Case 5.* Photomicrographs of three serial renal biopsies taken from case 5, ill with systemic lupus erythematosus.

A. Photomicrograph (Mallory × 400) of first biopsy taken in July, 1954. Note the severe interstitial edema and tubular degeneration. There is minimal thickening of the glomerular basement membrane.

2.6 mg./100 ml.; the blood urea nitrogen was 16 mg./100 ml., and nonprotein nitrogen was 35 mg./100 ml. The hematocrit was 21%; leukocytes were 7,900/mm^3. Examination of the bone marrow and peripheral blood for Hargraves' (L.E.) cells was negative. An intravenous pyelogram showed poor function; the urea clearance was 6 ml./min., and the creatinine clearance was 15 ml./min. The phenolsulfonphthalein excretion was 8% in 15 minutes.

Renal Biopsy (figure 4a): The sections contained a small segment of cortex (3 glomeruli) and some medulla. Distinct and diffuse thickening of the basement membrane was seen in these glomeruli. Hypercellularity, adhesions and crescents were not noted. Bowman's capsule was slightly thickened. The convoluted tubules appeared somewhat atrophic. A few collecting tubules contained red blood cells and casts. The interstitial fibrous connective tissue was distinctly edematous and contained a moderate number of inflammatory cells. The vessels were normal; fibrinoid changes were not seen in the glomeruli or in the blood vessels. Hematoxylin bodies were not seen. A Mallory-Azan preparation confirmed the thickening of the basement membrane, which stained blue as for hyaline thickening.

Histologic Diagnosis: Membranous glomerulonephritis.

In hospital she received one pint of blood, a diet low in salt and high in protein, and a course of tetracycline. After discharge from hospital she complained of persistent lethargy. The proteinuria and hematuria continued. In July she lost much hair from her head.

Second Admission: On September 17 she noticed marked swelling of the legs following an upper respiratory infection, and was re-admitted to hospital on October 4. She was anemic and had edema of the face, sacral area and legs. The liver was tender and was enlarged four fingerbreadths below the costal margin. Longitudinal ridging was noticed on the finger nails. On ophthalmoscopy a grade II retinopathy (Keith-Wagener) was noted. Arthritis of the left ankle appeared and lasted one week. She had several attacks of Raynaud's phenomenon.

The urine was loaded with erythrocytes. Hyaline, granular, red and white cell, and fatty casts were numerous. *Escherichia coli* and enterococci were grown on the culture and treated with Gantrisin. The 24 hour urine contained 23.6 gm. of protein. The hematocrit was 20%; the blood creatinine was 3.3 mg./100 ml., and the nonprotein nitrogen was 35 mg./100 ml. The other biochemical and renal function tests showed little change.

Second Renal Biopsy (figure 7b): The sections contained adequate cortex (9 glomeruli) and a little medulla. The glomeruli were ischemic. A distinct but irregular thickening of the basement membrane was noted. Focal areas of hypercellularity were seen in the glomeruli, and many were lobulated. A suggestion of wire looping was noted in some glomeruli. Neither adhesions nor epithelial crescents were noted in Bowman's spaces. Bowman's capsule was slightly thickened and fibrous. The tubules were moderately atrophic, and degenerative changes were seen in the lining epithelium of some. A few tubules contained chronic inflammatory cells within their lumina. The interstitial fibrous connective tissue was distinctly increased in amount and somewhat edematous, and contained scattered, small foci of chronic inflammatory cells. The blood vessels were not remarkable.

Microscopic Diagnosis: Subacute glomerulonephritis, Ellis type II, consistent with an advanced stage of renal involvement in lupus erythematosus.

After her discharge from hospital on November 2 her strength improved. In January, 1955, arthralgia affected the joints of the hands. The hematuria, still present, increased in amount following a sore throat.

Third Admission: On February 7 she was admitted to hospital for the third time. The pulse rate was 84/minute, and the blood pressure was 140/80 mm. Hg. A soft systolic murmur was heard at the apex. No other abnormality was found

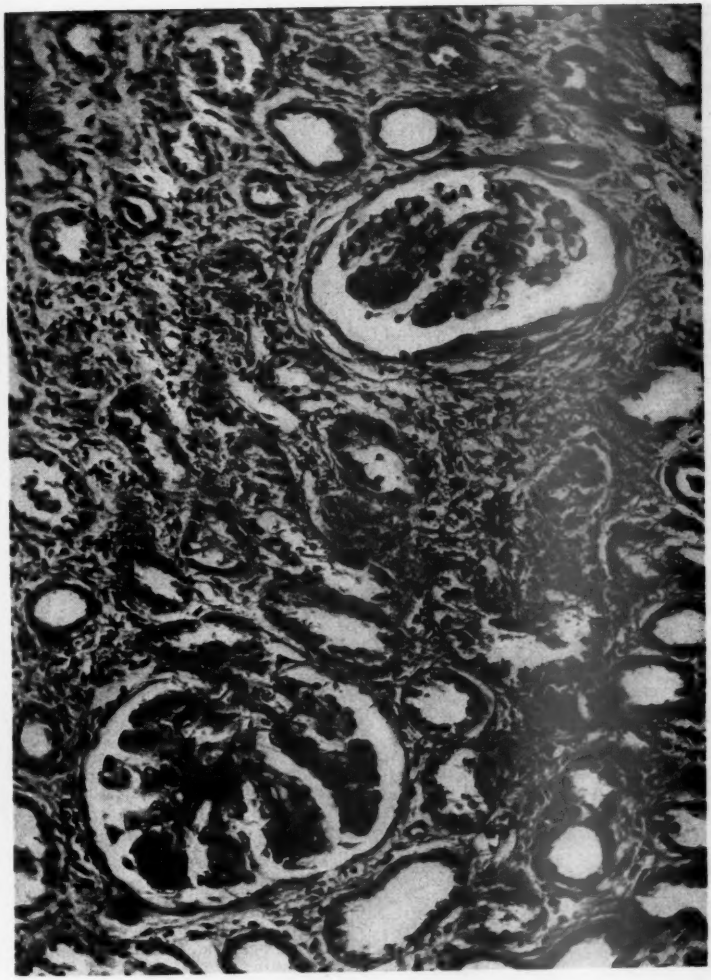

FIG. 7B. *Case 5.* Photomicrograph (H. and E., × 225) of second biopsy taken in October, 1954, when the nonprotein nitrogen level was elevated and there was marked impairment of renal function. Note that the interstitial tissue is edematous and contains foci of inflammatory cells. The glomeruli are hypercellular, ischemic and lobulated.

FIG. 7C. *Case 5.* Photomicrograph (H. and E., × 225) of third renal biopsy taken in February, 1955. Note the distinct epithelial crescent. There is definite thickening of the basement membrane of the glomeruli. The interstitial tissue is edematous and fibrosed. Numerous chronic inflammatory cells are present.

in heart or lungs. The liver was palpable two fingerbreadths below the right costal margin; the spleen was not felt.

Gross hematuria was still present, and there were 11.5 gm. of protein in a 24 hour urine specimen. The urine sediment contained numerous erythrocytes, a few leukocytes and a moderate number of casts of all types. Culture yielded a mixed bacteria flora, for treatment of which she received tetracycline. The total serum protein was 5.4 gm./100 ml. (albumin, 3.6 gm.; globulin, 1.8 gm.); the serum cholesterol was 326 mg./100 ml.; the blood creatinine was 4.7 mg./100 ml.; and the nonprotein nitrogen was 41 mg./100 ml. There was hyperchloremic acidosis (CO_2, 18 mM./L; chloride, 122 mEq./L.). She concentrated her urine to 1.012, and excreted only 4% of phenolsulfonphthalein in 15 minutes.

Third Renal Biopsy (figure 7c): The sections contained a small fragment of cortex (4 glomeruli) and no medulla. A diffuse thickening of the basement membrane was seen in the glomeruli. This was focally severe and suggested "wire looping." Mild focal hypercellularity was noted. In one Bowman's space a well formed epithelial crescent was seen. The tubules were markedly atrophic, but no distinct degenerative changes were observed in their lining epithelium. The interstitial fibrous connective tissue was markedly increased, slightly edematous and rather heavily infiltrated with inflammatory cells. Several small arteries had a moderately thickened wall, but no fibrinoid changes were seen.

Microscopic Diagnosis: Chronic glomerulonephritis, consistent with lupus erythematosus disseminatus. Although an occasional epithelial crescent was seen in this specimen, the dominant glomerular changes were still those of membranous glomerulonephritis (Ellis type II).

Comment

This case illustrates the progression of renal lesions in lupus erythematosus disseminatus. The patient had the nephrotic syndrome, which may be less rare than has been suspected. In our series of 32 patients with L.E.D., five had the nephrotic syndrome; three others had all the clinical features of the nephrotic syndrome, except that the serum cholesterol was very low ("pseudonephrotic syndrome"). In these patients the histologic findings in the kidney and the clinical course differed from that described above. The patients were gravely ill and died within a few weeks of developing edema.[18]

At present the patient described above presents many of the features of chronic Bright's disease. She does not have a skin rash. In other cases of L.E.D. the skin rash disappeared when the kidney became involved. These observations lead us to speculate that some cases of chronic glomerulonephritis may in fact have L.E.D.

The natural history of the renal lesion in lupus erythematosus disseminatus ("lupus nephritis") is shown schematically in figure 8. In brief, we have observed the appearance and progression of two types of glomerular lesion. The first, a local glomerulitis, progresses to subacute glomerulonephritis with crescent formation. The second begins as a thickening of basement membrane, and wire loops may be seen. It may pass into membranous glomerulonephritis.[28] Correlations have been made between urine findings and the pathologic changes (table 5). Cases with local or gen-

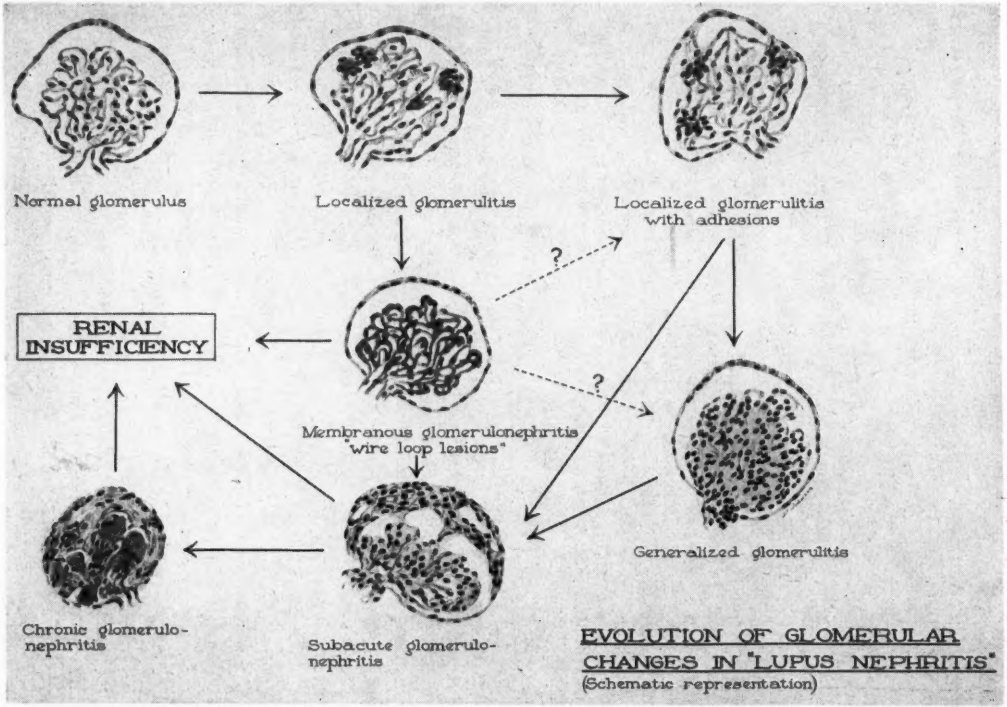

FIG. 8. This chart is a schematic representation of the histologic evolution of glomerular changes in lupus nephritis as reconstructed from serial biopsy studies.

eralized glomerulitis have white cells in the urine and may be mistaken for pyelonephritis.

Study of autopsy material suggests that in the pre-steroid era most of the deaths were due to secondary infection; at present, patients are dying of renal failure. This may be due to increased longevity, to the effects of steroids, or to the joint effects of steroids and broad spectrum antibiotics.

Reversible Lesions of the Glomerulus

Early in this paper we indicated that infectious diseases involving the glomerulus could be successfully treated with antibiotics. Healing and recovery of the glomerulus occurred. That severe lesions of the glomerulus can be repaired portends well for the future of these and other patients.

Table 5

Lupus Erythematosus Disseminatus: A Correlation of Urinalysis and Tests of Kidney Function with Renal Histology *

	Normal	Glomerulitis	Sub. Glom. Nephritis	Chr. Glom. Nephritis
Sp. Gr.	1.016–32	1.016–25	1.017–22	1.010–15
Alb.	0	1+	4+	4+
Casts	Few granular	Hyaline Granular WBC	Hyaline Granular Fatty OFB	Hyaline Granular Broad
Cells	0	5–8 RBC 14–46 WBC	10–20 RBC 2–5 WBC	5–10 RBC Occ.
PSP	28–48%	30–41%	13–22%	7–17%
Ur. Cl.	40–70 c.c.	40–60 c.c.	5–16 c.c.	5–15 c.c.
BP	Normal	Normal	Normal	Elevated

* Based on 42 biopsies in 26 patients.

Besides infections, reversible lesions have been observed in the kidneys of women with preëclampsia.[30] The following case illustrates the spontaneous recovery of glomerular lesions following delivery:

Case 6. A 29 year old housewife was found to have ankle edema, raised blood pressure and proteinuria in the last month of her second pregnancy (figure 9, table 6). A renal biopsy was done. The glomerular capillary walls were abnormal. Two months after delivery, normal renal tissue was found in sections from a second biopsy.

The patient was admitted to hospital on December 3, 1954. She was eight months pregnant and had first attended for antenatal care four weeks previously, when protein, red cells, and fine and coarse granular casts were found in the urine. At the time of her admission she had ankle edema and a blood pressure of 150/90 mm. Hg. She had no past history of renal disease, and her one previous pregnancy had been uneventful. The essential findings are shown in table 6.

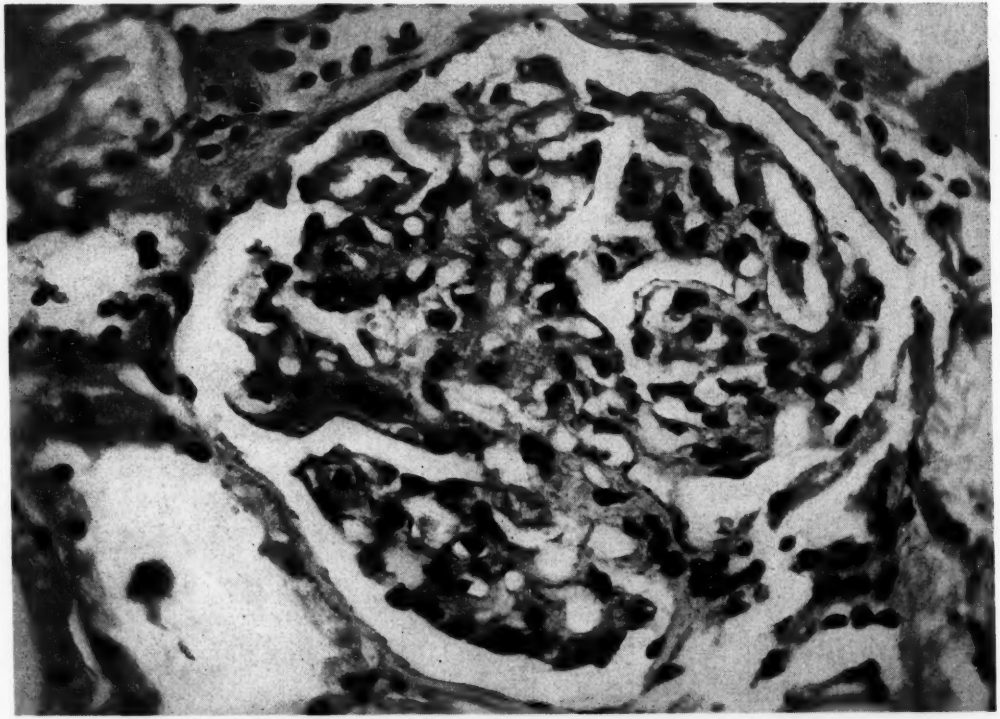

FIG. 9. *Case 6.* Photomicrographs (H. and E., × 600) of two renal biopsies, the first taken during toxemia of pregnancy and the second nine weeks after the delivery of the baby.

A. First biopsy, taken during toxemia of pregnancy. Note the edematous and smudgy appearance of the glomerular capillary membrane.

pregnancy and the second nine weeks after the delivery of the baby.

A. First biopsy, taken during toxemia of pregnancy. Note the edematous and smudgy appearance of the glomerular capillary membrane.

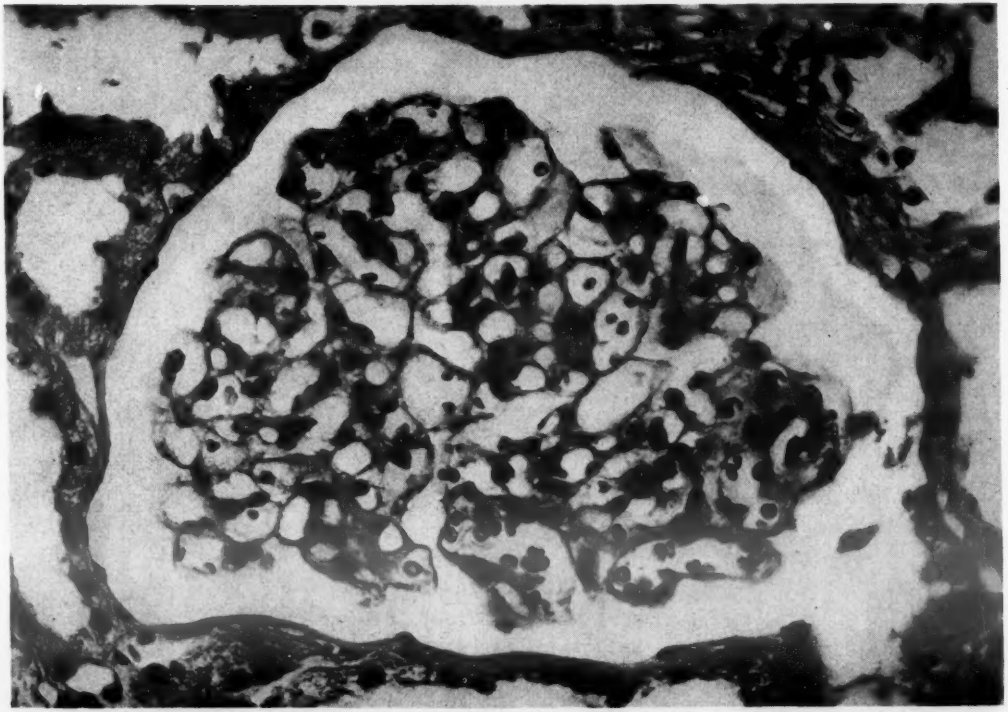

FIG. 9B. *Case 6.* Second biopsy, taken after toxemia of pregnancy. The glomerulus is entirely normal.

Renal Biopsy (figure 9a): A renal biopsy was made on December 11. Culture was negative. Adequate cortex (5 glomeruli) and no medulla were included in the sections. The glomeruli presented varying degrees of basement membrane swelling and appeared somewhat ischemic. There was no increase in their cellularity. Bowman's spaces and capsules were normal. The convoluted tubules varied in size, and many contained proteinaceous material. There were some vacuolation and granularity of the cytoplasm of the lining cells. The interstitial tissue was not remarkable, and no changes were seen in the blood vessels.

Microscopic Diagnosis: Changes consistent with eclampsia.

Postpartum Course: Two days after the biopsy the patient was delivered of a healthy female child, and she was re-admitted to hospital seven weeks later, on February 27. Her blood pressure was 130/80 mm. Hg, and there was no edema. She had no symptoms, and physical examination was normal. The essential findings are shown in table 6.

Second Renal Biopsy (figure 9b): A second renal biopsy was made on February 27. The section contained adequate cortex (5 glomeruli) and medulla. The glomeruli were entirely normal. There was no hypercellularity, and the basement membrane was thin and delicate. The blood vessels and interstitial fibrous connective tissue showed no changes.

Microscopic Diagnosis: Normal renal tissue.

TABLE 6

Clinical and Laboratory Findings in a 29 Year Old Housewife (Case 6) during and after Toxemia of Pregnancy

Clinical and Laboratory Findings	First Biopsy*	Second Biopsy†
Blood pressure (mm. Hg)	160/110	130/80
Weight (lbs.)	124	106
Ankle edema	2+	0
Microscopic urinalysis		
Cells/H.P.F.	5–8 WBC	0
Casts/H.P.F.	Few hyaline and cellular	Rare fine granular
Proteinuria (G/24 hrs.)	7.25	0
Serum albumin (G/100 ml.)	3.0	4.4
Serum cholesterol (mg./100 ml.)	365	313
B.U.N. (mg./100 ml.)	16	8
Sp. gr. concentration test	1.036	1.032
PSP (15" excretion)	41%	57%
Urea clearance (2 hr.)	32 ml./min.	45 ml./min.

* Taken 2 days before delivery of a healthy child.
† Taken 9 weeks post partum.

COMMENT

In the first biopsy, the swelling seen in the glomerular basement membrane and the absence of other glomerular changes were considered to be consistent with the usual findings in eclampsia. The basement membrane appeared to be swollen, edematous and smudgy, rather than dense and thickened, as is seen in cases of membranous glomerulonephritis. Periodic acid-Schiff preparations for mucopolysaccharides confirmed the observations that the basement membrane changes were due to swelling and edema rather than to a deposition of mucopolysaccharides. In the second biopsy the glomerular and tubular changes had entirely disappeared, indicating that the renal changes observed in the first biopsy were reversible.

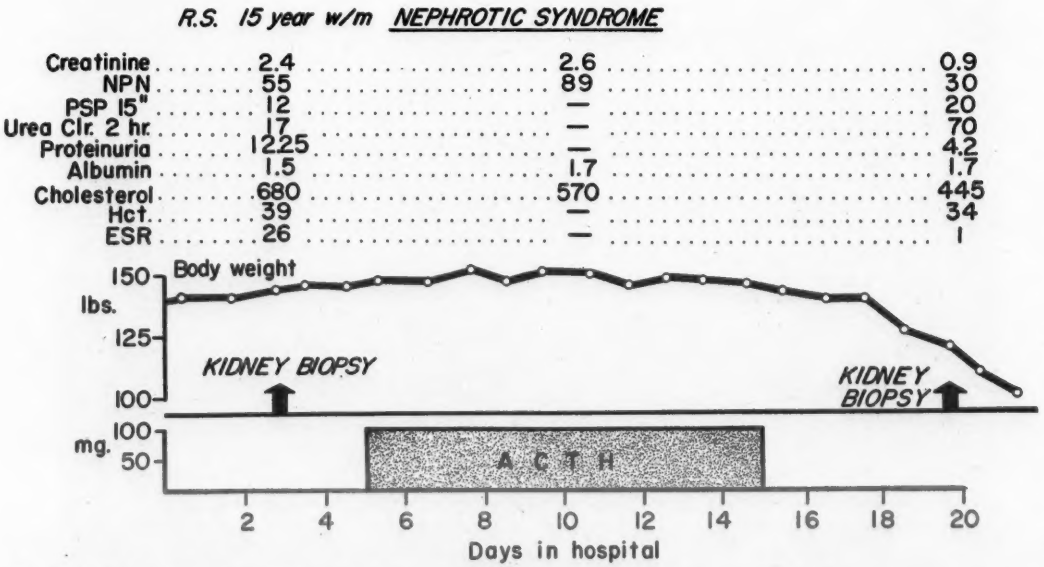

FIG. 10. *Case 7.* This chart illustrates the clinical course of a 15 year old schoolboy who had the nephrotic syndrome. Renal biopsies were taken before and after ACTH therapy.

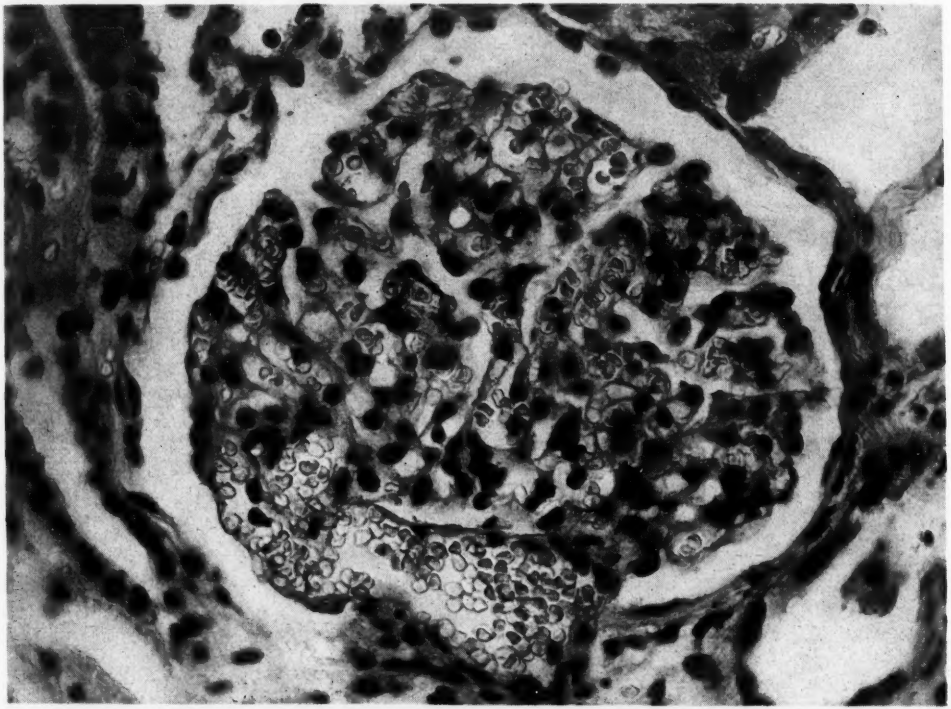

FIG. 11A. *Case 7.* Photomicrograph (H. and E., ×720) of renal biopsy taken before ACTH therapy. Note the marked congestion of glomerular capillaries.

Note the marked congestion of glomerular capillaries.

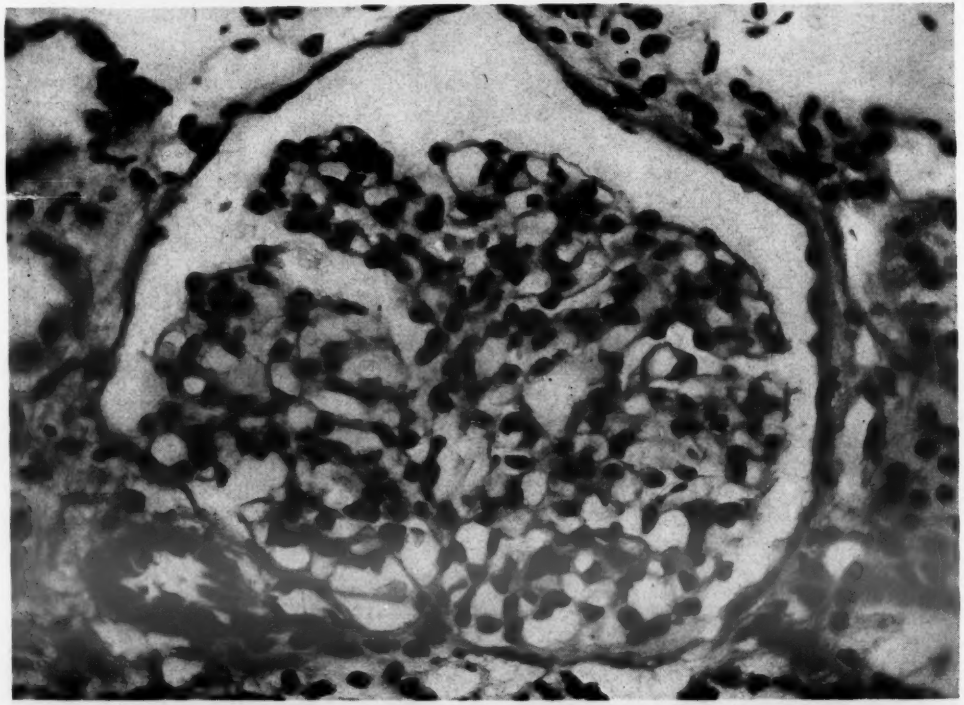

FIG. 11B. *Case 7.* Photomicrograph (H. and E., × 720) of renal biopsy taken after ACTH therapy and at the height of diuresis. The glomerulus is no longer congested and appears normal.

Renal Biopsy as a Pathophysiologic Tool

The rapid extraction of a core of renal tissue provides living cells which can be instantaneously preserved in liquid nitrogen. These cells can then be studied at leisure by a number of microbiochemical technics.[41, 42] In addition, cytochemical and histologic studies can be made on such tissue. For example, Bjørneboe et al.[20] have shown that alkaline phosphatase in the brush border of tubular cells may decrease during the course of the nephrotic syndrome.

A better understanding of the intimate pathophysiology of the nephron will eventually lead to improvements in the diagnosis and management of renal diseases. Some pathophysiologic changes in the kidney are discussed in relation to the following case of the nephrotic syndrome:

Case 7. A 14 year old, rather bucolic high school student had enjoyed good health until June, 1954, when he gradually developed anasarca (figures 10, 11 and 12). In January, 1955, physical examination revealed pallor and anasarca. The blood pressure and funduscopic examination were normal. Urinalysis revealed gross proteinuria, microscopic hematuria, cylindruria, and many doubly refractile bodies in the urine sediment. Renal biopsy was done before a course of ACTH and at the height of diuresis following treatment with ACTH.

A 14 year old high school student was referred to hospital by Dr. Mullinex. He had enjoyed good health until June, 1954, when his ankles began to swell at night. The swelling progressed until the entire body was edematous. No sore throat, respiratory infection or other infection preceded this illness. In July he was treated with ACTH for seven days for the nephrotic syndrome and lost 30 pounds in weight. Edema gradually reaccumulated. In December, 1954, oliguria was noted. He had no gross hematuria, back pain, nocturia or burning on urination.

On physical examination he was depressed, pale and bloated. He was edematous to the hips and had swelling of the face and upper limbs. His weight was 147 pounds. Funduscopic examination was normal, and the blood pressure was 110/70 mm. Hg. The pulse rate was 84. The thyroid was slightly and diffusely enlarged. The lungs were clear. The heart was not enlarged; the sounds were of good quality; no murmurs were heard. The liver and spleen were not felt. There was no tenderness over the kidneys. Neurologic examination was normal.

Laboratory Data: The specific gravity of the urine was 1.032; there was 4 plus proteinuria (5.6 gm. per 24 hours), and no reducing substance or acetone was found. Many oval fat bodies, doubly refractile bodies, hyaline, granular and cellular casts, and erythrocytes were seen in the centrifuged urine sediment. The hematocrit was 39%, and the erythrocyte sedimentation rate was 26. The leukocyte count was 9,050 per mm^3, with a normal differential count.

In the blood, the nonprotein nitrogen was 55 mg./100 ml.; the blood urea nitrogen was 34 mg./100 ml., and the creatinine was 2.4 mg./100 ml. In the serum, the protein was 4 gm./100 ml. (albumin, 1.5, and globulin, 2.5 gm./100 ml.); the cholesterol, 608 mg./100 ml.; the sodium, 142 mEq./L.; the potassium, 5.7 mEq./L.; the chloride, 97 mEq./L., and the CO_2 combining power was 17 mM/L. The 15 minute excretion of phenolsulfonphthalein was 12.5%. The urine concentrated to a specific gravity of 1.036. The urea clearance was 17 ml./min. The kidneys were enlarged on an intravenous pyelogram. They excreted Diodrast normally.

On January 5, 1955, a percutaneous biopsy was taken from the right kidney. Two days later a 10 day course of ACTH (100 mg. daily) was started. During this time the blood nonprotein nitrogen increased to 89 mg./100 ml. Three days

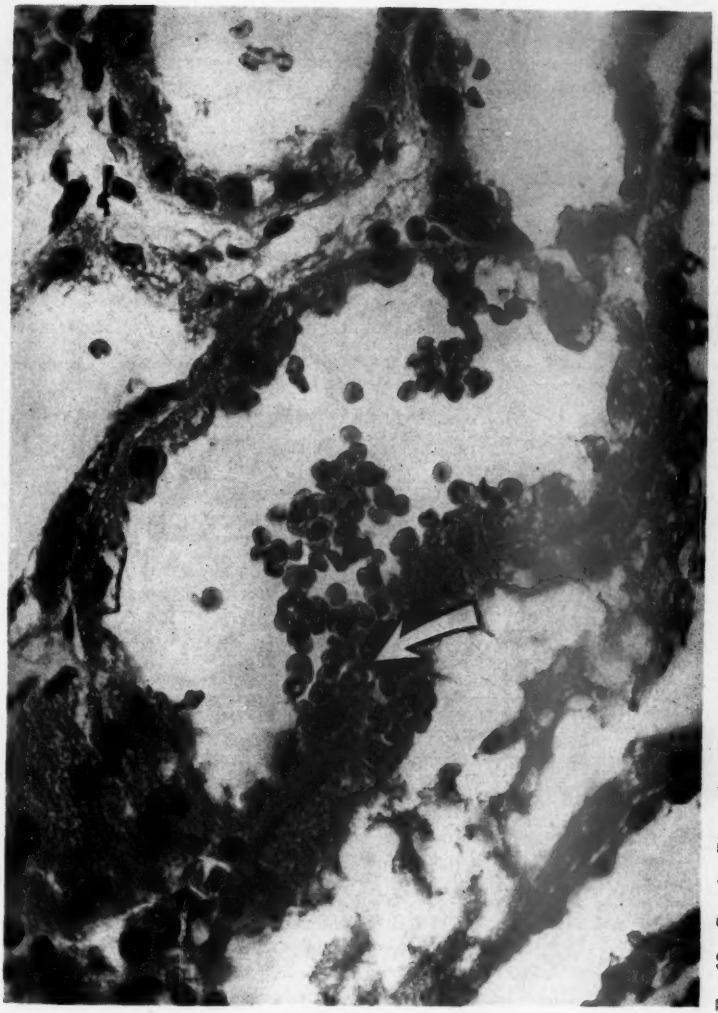

FIG. 12. *Case 7.* Photomicrograph (H. and E., × 1200) of first renal biopsy showing the passage (see arrow) of erythrocytes from the peritubular capillaries into the tubular lumen.

after stopping ACTH diuresis commenced; he lost 46 pounds in five days. He was greatly improved. The blood nonprotein nitrogen was 30 mg./100 ml.; the 15 minute excretion of phenolsulfonphthalein was 20%; a total of 4.2 gm. of protein was found in the 24 hour specimen of urine, and urea clearance was increased to 70 ml./min. The serum proteins were unchanged, and the serum cholesterol level fell to 445 mg./100 ml. The erythrocyte sedimentation rate was 1 mm. per hour, and the hematocrit dropped to 34%. A second renal biopsy was taken at the height of diuresis on January 22, 1955. The patient was discharged much improved.

Renal Biopsies (figures 11a and 11b and table 7): First Biopsy: The sections contained adequate cortex (8 glomeruli) and a small segment of medulla. All glomeruli were seen to be markedly congested and distended and filled with red blood cells. There was no hypercellularity or thickening of the basement membrane. Slight lobulation but no other changes were seen in one glomerulus. The tubules were dilated, and the lining epithelium was low cuboidal, or flat. Vacuolation and granularity of the cytoplasm were noted in some of these cells. Many well pre-

TABLE 7

A Comparison of the Histologic Findings before and during Diuresis Induced by ACTH in a 15 Year Old Schoolboy (Case 7) Ill with the Nephrotic Syndrome Due to "Lipoid Nephrosis"

	Jan. 5, 1955	Jan. 21, 1955
	ACTH Therapy Jan. 8, 1955 — Jan. 17, 1955	
Glomeruli	Congested, enlarged	Normal
Bowman's space	Proteinaceous material, no RBC's, hyperplastic epithelial cells	Small amount of proteinaceous material
Interstitial tissue	Interstitial edema, few inflammatory cells	No edema, no inflammatory cells
Tubules	Flat epithelium with RBC's in dilated lumina	Taller tubular cells with smaller empty lumina
Vessels	Engorged peritubular vessels Edema of arterioles	Normal

served red blood cells were seen in a few tubular lumina. The peritubular capillaries were congested, and in at least one area red blood cells were seen extending from ruptured peritubular vessels, through the altered tubular epithelium, into a tubular lumen (figure 12). In other tubules, proteinaceous material was seen. No free red blood cells were seen in Bowman's spaces. Bowman's capsule was normal in appearance. The interstitial fibrous connective tissue was markedly edematous and contained several small foci of chronic inflammatory cells. The walls of some of the small arteries were slightly thickened, apparently due to edema; the other arteries were not remarkable.

Microscopic Diagnosis: Tubular disease, type undetermined.

Second Biopsy: The sections contained adequate cortex (12 glomeruli) but no medulla. The glomeruli were normal except for a suggestion of focal hypercellularity. A normal number of red blood cells was found within the capillaries. Proteinaceous material was seen in Bowman's space, but the capsule was completely normal. Many of the tubular cells were swollen, and vacuolation of their cytoplasm was evident. Cuboidal epithelium without distinct alterations was seen in other

tubules. Proteinaceous material was seen in many of the tubular lumina. The interstitial tissue was slightly increased in amount and slightly edematous in some areas. Occasional inflammatory cells were noted. The blood vessels were normal.

Microscopic Diagnosis: Focal tubular disease, type undetermined.

Comment

In the first biopsy all the glomeruli were markedly congested and distended and filled with erythrocytes. The peritubular capillaries were also greatly congested, and many well preserved erythrocytes were seen in some of the tubular lumina. No red blood cells were seen in Bowman's space, but in one area erythrocytes were seen extending from a ruptured peritubular vessel through the altered epithelium into the tubular lumen (figure 12). In our biopsy material it is unusual to find only a few erythrocytes in the glomerular capillaries, even in glomerulonephritis.[43] We have never seen free red blood cells in Bowman's space, except in one patient with essential hematuria. However, in a large percentage of biopsies taken from patients with hematuria, free red blood cells and erythrocyte casts have been observed in proximal and distal convoluted tubules. For many years we have all been taught that renal hematuria was due to bleeding from the glomerulus. This teaching is based on examination of autopsy material. The observations described above lend support to the idea that, in some instances, hematuria is the result of bleeding directly into the tubular lumina. In case 7, at least, the hematuria was the result of rupture of a peritubular capillary.

There is no doubt that the regression of histologic changes seen in the second biopsy was the result of giving ACTH. These were: loss of edema, disappearance of glomerular and peritubular vascular congestion, an increase in height of the tubular cells, and a decrease in the diameter of the tubular lumina. Exactly what caused this is not known, but it must be due to some functional effect of steroid hormones, rather than to an effect on structure. Whether the hormone increased glomerular permeability or whether it altered blood flow in the glomerulus so that a cell-poor fraction of blood coursed through these tiny vessels must remain speculative. Either effect could rid the body of water.

The height of the tubular cells has been thought to vary with the state of diuresis. Maximow and Bloom [44] observed that the tubular cells are flat with diuresis and tall with a small urine output. In our patient the tubular cells increased in height during massive diuresis. This observation has been reported once before, by Bjørneboe et al.,[37] who noted low epithelium in a patient with the nephrotic syndrome due to "genuine nephrosis" and a tall blurred epithelium during diuresis following ACTH therapy.

Renal Biopsy and the Problems of Proteinuria

The means by which the plasma protein passes from the blood to the urine are the center of controversy. One school considers that the ap-

pearance of protein in the urine is due to an increased permeability of the glomerular membrane. The other view is that there is a disturbance of the normal and nearly complete reabsorption of the protein normally filtered by the glomerulus. This failure of tubular reabsorption causes proteinuria. One group of investigators claims that protein passes across cell membranes by a process of active diffusion. On the other hand, electron microscopy studies have demonstrated minute pores in the glomerular capillary basement membranes [45] and in the tubular cells.[46] This strengthens the concepts of Pappenheimer,[47, 48] who believes that plasma protein molecules pass out of the circulation through pores whose calculated size is of the same magnitude as that observed by Hall.[45] Whether protein can be secreted by the tubular cells or whether it can pass directly from the peritubular vessels into the tubular lumina is not known.

Renal biopsies have been done on a number of patients whose urines have been consistently free of protein. In the sections of biopsies from some of these patients proteinaceous material was readily seen both in Bowman's space and in the tubular lumina. These observations [26] confirm the concept that protein is filtered by the glomeruli and reabsorbed by the tubules. Studies of renal biopsy material with the electron microscope and microdissection may help to elucidate this problem.

Summary and Conclusions

Two hundred renal biopsies have been done in the prone position. No serious complications developed, and morbidity was slight. Cultures of the blood and tissue taken from the kidney were made in all cases. Five patients were observed in whom urine cultures were repeatedly negative and in whom culture of the kidney tissue was positive. They all responded to treatment with antibiotics.

Analysis of the results demonstrates that this technic is a most useful tool in the diagnosis and management of diseases involving the nephron, the vessels, and the ground substance of the kidney. Case histories have been presented to illustrate the value of renal biopsy. In the nephrotic syndrome it is frequently difficult to give an accurate prognosis when the patient is first seen. Renal biopsy is of singular assistance in assessing prognosis in this condition.

Serial biopsy studies have enabled us to make a close clinicopathologic study of the natural history of diseases involving the kidney; they have been useful clinically in determining the response of the organ to treatment, and are proving of value in solving problems related to renal pathophysiology, such as the origin and mechanism of renal hematuria and proteinuria.

Summario in Interlingua

Esseva executate 200 biopsias renal in position pron. Nulle seriose complicationes resultava, e le morbiditate esseva leve. In omne casos culturas del sanguine e del texito obtenite ab le ren esseva executate. In 5 patientes le culturas ab biopsias renal

esseva positive ben que in lor casos culturas urinari habeva repetitemente remanite negative. Un de iste patientes es describite. Ille habeva un debilitante morbo febril con proteinuria e multe erythrocytos in le urina. Su functiones renal esseva grandemente reducite. Un typo inusual de glomerulonephritis esseva constatate per le biopsia, e enterococcos hemolytic esseva culturate ab le texito renal. Le patiente esseva tractate con tetracyclina, e ille recuperava completemente.

Biopsia renal ha essite de valor in diagnose e in therapia. Es describite un caso de hypertension maligne pro le qual le existentia de normotension quatro menses previemente esseva establite. Le diagnose de hypertension essential e de acute glomerulonephritis esseva prendite in consideration, sed le specimen bioptic demonstrava chronic pyelonephritis active. Le patiente esseva tractate a bon successo con antibioticos e agentes antihypertensive.

Quando patientes con le syndrome nephrotic es examinate initialmente, un exacte prognose es difficile a formular. In tal patientes biopsias renal ha essite de distinguite adjuta in prognosticar le curso del morbo. Es discutite duo patientes con le syndrome nephrotic. Al tempore del examine initial, le tractos clinic de illes esseva identic. In un de iste casos glomerulonephritis membranose esseva constatate: in le altere le diagnose esseva sever degeneration tubular. De accordo con le prediction super le base de specimens bioptic, le prime patiente deteriorava progressivemente, durante que le altere ha progredite incoragiantemente.

Le historia natural de morbos que involve le ren ha essite sequite per medio de biopsias in serie. Detaliate studios clinicopathologic ha essite executate. Es describite un studio executate in un femina de 33 annos de etate suffrente de lupus erythematose disseminate. In iste morbo duo typos de lesiones glomerular esseva observate. Le un comencia como un glomerulitis local e progrede a glomerulonephritis subacute con formation de crescentes. Le altere comencia como un spissification del membrana basal e pote devenir chronic glomerulonephritis membranose.

Le responsa del ren al tractamento con ACTH ha essite studiate. Es discutite problemas de pathophysiologia renal, como per exemplo le origine e le mechanismo de hematuria e proteinuria renal. Nos ha monstrate que le technica del biopsia renal es de grande valor in le diagnose, therapia, prognose, e manipulation de patientes con morbos que involve le ren. Nos ha etiam monstrate que iste technica es non riscose, providite que illo es applicate caute- e exactemente.

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CASE REPORTS

ESSENTIAL CRYOGLOBULINEMIA *

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DURING the past two decades numerous reports have appeared in the medical literature describing a serum protein which precipitates on exposure to cold.[1, 2, 9, 14, 22, 23, 34, 35, 38, 42, 46] This protein has been called cryoglobulin, and occurs in association with or secondary to a variety of disease processes. It is our purpose to report an unusual case of cryoglobulinemia, under our observation for three years, in which no such underlying disease was found present (table 1).

TABLE 1

"Essential" Cryoglobulinemia

1. Clinical Features
   a. Long history
   b. Signs and symptoms associated with capillary thromboses on surfaces exposed to cold
      1. Acropurpura
      2. Ulcers, especially lower extremities
      3. Urticarial reactions
      4. Conjunctival, oral, nasal hemorrhages
   c. Absence of other disease
2. Laboratory Findings
   a. Cryoglobulinemia in significant amounts (500 mg. or over per 100 ml. of serum)

CASE REPORT

A 45 year old white housewife was first seen in September, 1951, complaining of cold urticaria. Her symptoms were aggravated during the cold months and when handling frozen foods. She dated her tendency to symptoms from chilling since childhood. In the summer of 1950 she first noted giant hives during damp and windy days, and during the winter of the same year she also developed a prominent purpura of both lower extremities. The purpuric spots disappeared spontaneously after 10 to 14 days.

In 1951 her symptoms became progressively worse. Urticaria then appeared after bathing (in Florida). Localized wheals were noted when her skin came into contact with a metal chair or bedpan. Abdominal pain followed the drinking of ice water.

Allergic investigation revealed few positive findings. The patient was extremely tense and irritable, and subject to severe migraine headaches. Systemic review was essentially negative except for a cholecystectomy performed in 1946. Physical ex-

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From the Departments of Medicine and Allergy, Grace Hospital and Sinai Hospital, Detroit, Michigan.

amination revealed no significant physical findings. Heart and lungs were normal. The blood pressure was 110/60 mm. of Hg. The skin showed urticarial wheal reaction to even momentary surface application of an ice-filled glass.

The patient was given an opportunity to discuss her personal problems, and there ensued a short period of seeming improvement in the migraine. A month later the patient had a severe exacerbation of her headaches and was given five 1 mg. tablets of ergotamine tartrate. This was followed by severe painful purpura involving the flexor and medial surfaces of the arms, forearms, thighs, legs and ankles. On another occasion 0.5 mg. of this drug administered subcutaneously produced dizziness and nausea as well as extensive purpura (figure 1).

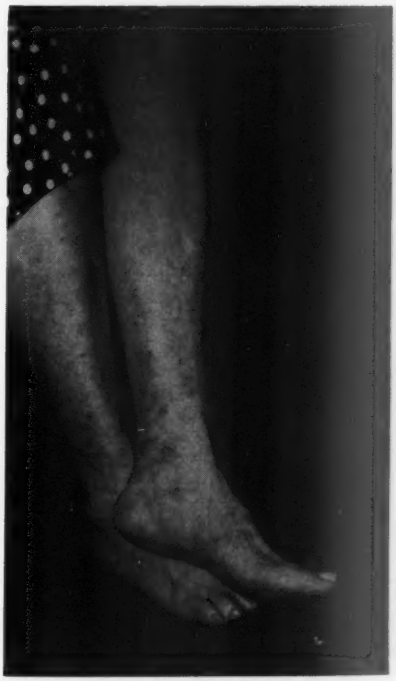

FIG. 1. Purpura of the lower extremities as noted in 1951.

The patient was then admitted to the Grace Hospital for study. The physical examination again revealed no general abnormalities. Complete laboratory investigation also was essentially normal except for the increased sedimentation rate and the high blood proteins.

Laboratory Data: Hemogram: hemoglobin, 11.5 gm. per 100 ml. of blood; red blood cells, 3.14 million per cubic millimeter of blood; white blood cells, 6,200 per cubic millimeter of blood; differential count revealed 68% polymorphonuclear leukocytes, 31% lymphocytes, and 1% eosinophils. Hematocrit showed 34% packed red cells. The platelet count was 325,000. Coagulation time as well as the prothrombin

time and bleeding time was normal. The erythrocyte sedimentation rate was 88 mm. per hour (Westergren, corrected). Sedimentation rate subsequently repeated at 20° C. was 33 mm. per hour, and at 37.5° C. was 45 mm. per hour. The total serum protein was 10.7 gm.; albumin, 4.1 gm.; total globulin, 6.6 gm., of which cryoglobulin was 4.3 gm. Fibrinogen was .26%. Erythrocyte fragility in hypotonic saline: beginning hemolysis at .42%, complete at .28%. Kahn test negative. Cold agglutinin titer: 1:32 and 1:54. Vitamin C level: .72 mg. per 100 c.c. Gastric analysis showed a total acidity of 11° before exposure to cold and 14° after. Bromsulphalein liver function test, basal metabolic rate and the sternal marrow aspiration, as well as a test for L.E. cells, were entirely normal. Roentgenograms of chest, skull, paranasal sinuses and spine revealed no abnormality. Serial urinalyses were negative; there was no Bence Jones proteinuria.

The patient responded well to the protection afforded by hospital conditions and was discharged to her home. Benadryl was administered because of the symptomatic relief afforded by this drug, and because it effectively decreased whealing reaction to cold.

During this interim, biomicroscopic examination of the conjunctival vessels after contact exposure to a cube of ice wrapped in gauze was done with the aid of Dr. H. Pliskow. He noted definite constriction of the arterioles, sludging and segmentation of the column of blood. The nonexposed conjunctiva was entirely normal. Funduscopic examination showed no evidence of hemorrhage or other abnormality.

The patient was again admitted to the hospital on July 6, 1952, with exacerbation of all symptoms. Her hands swelled even from holding the hose to water the lawn. Her ankles and legs were markedly pigmented as a result of previous crops of purpuric and petechial lesions. The ears were also affected with fresh purpuric and petechial blotching. Laboratory studies showed no striking change from those reported above.

Bone marrow aspiration biopsies from both sternum and iliac crest again showed normal bone marrow. Particularly, no increase in myeloma or plasma cells was noted. Further roentgenograms of the spine and pelvis were again normal. The serum protein electrophoretic pattern was determined through the courtesy of Dr. M. Peterman, and the results are tabulated as follows:

TABLE 2

Relative Protein Concentration

	Albumin	a_1	a_2	B	γ	A/G
Asc.	54.5	3.5	10.5	14.7	16.8	1.2
Desc.	59.5	5.2	15.0	14.3	6.0	1.4
Average	57.0	4.3	12.7	14.5	11.4	1.3
Normal average	55.2	5.3	8.7	13.4	11.0	.9

This does not contain the cryoglobulin (precipitated).

Attempts at paper chromatographic measurement were unsuccessful because of precipitation of the cryoglobulin at the point of application of the serum to the paper strip. This was true both when the patient's serum was used and when cryoglobulin extracted and redissolved according to the method of Lerner and Greenberg [24] was employed.

ACTH was administered intravenously in the amount of 15 mg. in 1,000 c.c. of 5% dextrose in water during the first 24-hour period. Thereafter, cortisone, 100 mg., and ACTH, 40 mg., were given daily for six days. The absolute eosinophil count fell from 50 to 10 per cubic millimeter during this period. No appreciable effect on the urticaria was noted which could not be explained by the protection offered by hos-

pitalization. Since the packed volume of cryoglobulin dropped from 12% to 4% of the total serum during this period, some alteration of the amount of the cryoglobulin may have occurred.

The use of Priscoline was suggested by the exacerbation of symptoms to a vasoconstrictor, ergotamine tartrate. Priscoline orally, 50 mg. four times a day, resulted in early but inconstant improvement.

The patient was again hospitalized in the spring of 1953. Besides numbness and purpura there also appeared painful thrombotic necrotic areas in the external ear as well as the lower extremities. She also complained of severe pressing pain of short duration in the chest anteriorly which frequently caused her to faint. Blood pressure recorded April, 1953, was 100/70 mm. of Hg.

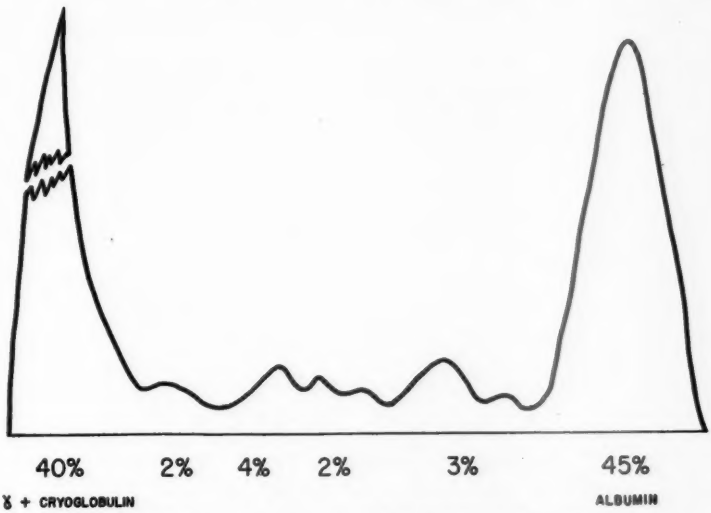

FIG. 2. Graph from densitometric readings of a paper electrophoresis of serum of patient, 1952.

At this time a prolonged course of ACTH, 25 mg. twice a day, and cortisone, 50 mg. three times a day, produced only a mild decrease in symptoms, although the cryoglobulin content of the serum had decreased to 0.1 gm.%.

Paper electrophoresis * separation was achieved during this period using the Kelab-AB, model 5K51 apparatus and hypertonic saline as a solvent for the cryoglobulin. The pattern is illustrated in figure 2.

During the summer of 1953 she made a fair adjustment, was seen only once, and "felt swell" during the heat wave. However, when the patient returned in September, 1953, following a period of illness at home, she complained of severe pain over frontal and occipital areas as well as over the precordium and extremities. She showed a blood pressure of 160/90 mm. of Hg, puffiness of the eyelids, severe mental depression, albuminuria, numerous pus cells and red blood cells per high power field,

* Paper electrophoresis was performed through the courtesy of Dr. N. K. Ressler, Wayne County General Hospital, Eloise, Michigan.

and severe anemia. No enlargement of the liver and spleen was found, but it was observed by the patient and her husband that her skin was not so cold to the touch as previously.

On admission to Sinai Hospital, Detroit, October, 1953, the patient again revealed the previously noted hypertension and abnormal urinary findings. A search for L.E. cells was negative. Muscle biopsy of the thigh showed no evidence of periarteritis. Sternal puncture again was not diagnostic, but the differential pattern was indicative of reactive myeloid leukocytic hyperplasia. The peripheral smear showed normocytic-normochromic anemia. An x-ray of the chest showed slight left ventricular enlargement. A transient pericardial friction rub was noted, but with no corresponding electrocardiographic changes. The patient improved under conservative treatment without resorting to the use of adrenocorticotrophic hormone.

Subsequently the patient was placed on low sodium diet, sedatives, iron and Dibenzylene, 20 mg. daily. Though cold sensitivity was markedly improved, the

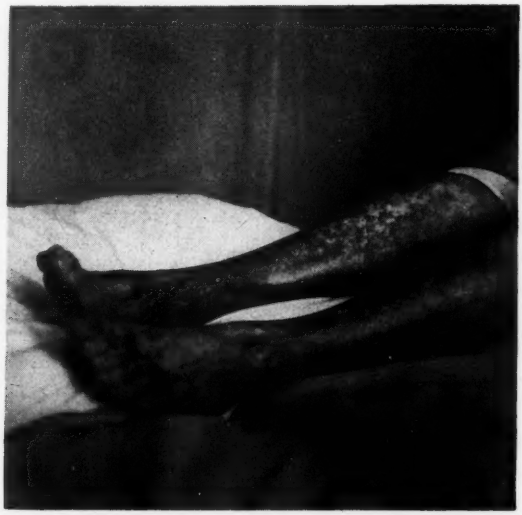

FIG. 3. Increased purpura and peripheral scarring as noted in 1954.

anemia was progressive. The red blood cell count was 2.29 million, and the hemoglobin was 7.5 gm. per 100 ml. of blood during February, 1954. She presented a blood pressure of 180/100 mm. of Hg, pitting edema, and a 15 pound weight increase.

The patient was admitted to Ford Hospital, Detroit, March, 1954, because of severe vomiting and headache.

Positive findings were: puffy face, retinal hemorrhage, crepitant râles—left base, grade 3 systolic blowing murmur near base of heart, questionable and transient pericardial friction rub. The peripheral scarring of the lower extremities was much increased by this date (figure 3).

The laboratory findings were: hemoglobin, 8 gm.; red blood cells, 2.70 million; white blood cells, 11,600 per cubic millimeter of blood; polymorphonuclear leukocytes, 93%; reticulocytes, 4.2%; nonprotein nitrogen, 35 mg.%; fasting blood sugar,

113 mg.%; cholesterol, 395 mg.%; carbon dioxide combining power, 20 mEq. The indirect Coombs' test was negative.

The urine showed 4 plus albumin with numerous white blood cells and red blood cells.

Peripheral smear showed normocytic anemia with adequate platelets. Sternal smear showed myeloid-erythroid ratio × normal—3.7 to 1. The plasma cell count increased to 4.2%. The L.E. test was negative.

Patient improved following several blood transfusions and cortisone, low salt diet, iron and Serpasil, .25 mg. twice a day.

Discussion

Cryoglobulinemia results in clinical manifestations of acropurpura, hemorrhage from the nose, gums and retina, Raynaud's syndrome, skin ulcerations and cold urticaria.[2, 32]

To demonstrate cryoglobulin in vitro it is necessary that the blood should be withdrawn from a vein in a *warm* syringe, incubated at 37.5° C. for at least one-half hour, centrifuged, and the separated serum placed in the refrigerator overnight. The cryoglobulin is then seen as a dense amorphous precipitate varying from a mere trace to a large percentage of the serum protein. The precipitate may occur with only slight drop in temperature below 37.5° C. Failure to incubate the blood following withdrawal results in the cryoglobulin's becoming enmeshed in the blood clot, and accounts for many cases escaping detection.[2]

The suspicion of cryoglobulinemia in the above instance was aroused by the high sedimentation rate in the absence of evidence of infection or neoplasm, by the presence of a gel-like appearance of the blood, and by the associated cold urticaria and purpura.

A brief historical review may be pertinent, since only nine such cases were reported until 1948. Wintrobe [47] was the first to report a case of myeloma with cold-precipitable serum, Raynaud's phenomenon, purpura and retinal hemorrhages. Shapiro and Ross [35] described a "viscous protein" in the serum of a patient with multiple myeloma. It was Lerner and Watson,[22] however, who in 1947 first coined the term "cryoglobulinemia" in describing a case with purpura, cold sensitivity and cold-precipitable serum globulin.

Lerner, Barnum, and Watson [23] studied the sera of 120 patients suffering from various pathologic conditions, and found cold-precipitable proteins present in 30 instances, the amounts varying from a trace to a concentration greater than 25 mg.%. Only one case was reported in the latter category. Hansen and Faber [11] reported a case of cryoglobulinemia with Raynaud's syndrome which at autopsy was diagnosed plasma cell leukemia.

Barr [2] and his associates reviewed the entire subject of cryoglobulinemia in 1950 and added two new cases; one with symptoms of cold sensitivity, Raynaud's syndrome, retinal hemorrhages and multiple myeloma, and the other with the same clinical manifestations but no primary etiology. In 121 cases of various disease entities such as multiple myeloma, Raynaud's syndrome, Hodgkin's disease and lymphosarcoma, Barr [2] reported a cryoglobulin level of 6 to 25 mg.% in eight cases, and traces in 10. Six of the eight positive cases had myeloma, one had leukemia, and one was undetermined (no bone marrow study was done). Besides the clinical manifestations of purpura, cold urticaria and

Raynaud's syndrome, other symptoms were also observed such as deafness, joint pain, anemia and renal disturbance. It may be noted that the blood serologic test for syphilis was negative in all cases despite the hyperglobulinemia.

Rorvik [32] in 1950 reviewed 10 cases of cryoglobulinemia and added one with associated myeloma. His case was also characterized by cold sensitivity and hypostatic purpura. On microscopic examination of a drop of serum allowed to dry on a glass slide he noted needle-shaped crystals. (Sera of two patients with cryoglobulinemia were compared by us with 10 control sera. No significant difference was noted on drying either at 37.5° C. or room temperature.)

The case presented here follows the main clinical features previously described. A number of observations deserve comment. It was noted on four occasions when our patient was given ergotamine tartrate that the purpuric manifestations were markedly aggravated. Since this effect in all instances occurred within 24 hours of the administration of the drug, one must assume a causal relationship. It is likely that the purpura resulted from the vasoconstriction and consequent slowing of blood circulation through terminal arterioles and capillaries. However, the purely toxic effects of the ergotamine itself cannot be entirely excluded. The mechanism of production of purpura and cold urticaria in cryoglobulinemia is not definitely established. Several possible causative factors have been suggested by Rorvik: [32, 33] (1) increased blood viscosity; (2) precipitation of cryoglobulin in peripheral vessels; (3) intravascular agglutination of erythrocytes; (4) amyloid degeneration in the vascular walls with abnormal fragility (in myelomatosis only); and (5) fibrinogenopenia.

The effects of ergotamine tartrate in this case suggest that the precipitation of globulin in peripheral capillaries is by far the most important of the above factors. The observation of sludging in conjunctival vessels as a result of cold exposure also supports this explanation. The fact that purpura involves more frequently the lower extremities may be due more to the cooler skin temperatures and greater degree of exposure than to the hypostatic effect.[34]

High viscosity is not an adequate explanation for the production of purpura, since hyperglobulinemia does not in itself lead to purpuric reactions. Flemberg and Lehmann [21] have, moreover, pointed out that high viscosity does not necessarily parallel the degree of hyperglobulinemia.

The sedimentation rate was unusually elevated in our case, and indeed was one of the unexpected findings responsible for focusing our attention on this clinical entity. The rise in the sedimentation rate at 37.5° C. over that at 20° C. is consistent with reports by other observers.[37] Our reported values agree closely with expected effects of temperature on erythrocyte sedimentation according to the correction curves devised by Wartman.[44] However, several exceptions are reported on the relation of the sedimentation rate to degree of temperature, some finding that the higher the temperature the lower the sedimentation rate. Rorvik [32, 33] states that conditions which show a strong tendency to cold agglutination show a considerable similarity to cases of cryoglobulinemia. In cold agglutination, however, the sedimentation rate is lower at 37° C. than at room temperature. Thus the sedimentation rate may be used to differentiate cryoglobulinemia and cold agglutination. The associated cold agglutination present in some may account for the atypical sedimentation rates reported in cryoglobulinemia.

An electrophoretic curve from paper chromatography (figure 2) shows a considerable rise in the globulin content of the serum, particularly the gamma fraction. No abnormal (para-gamma) globulin peak, however, was observed.[1, 29, 35]

Special allergic studies were carried out and were reported in detail.[38] The conclusions may be summarized as follows:

1. Passive transfer studies to cold urticaria were negative.
2. Passive transfer studies with a nonpurified cryoglobulin fraction were positive.
3. Benadryl as a representative of antihistamines definitely reduced the whealing reaction.
4. The phenomenon of exhaustion of antibodies was suggested by the refractoriness of the exposed sites to further cold exposure.

It may be noted that the degree of clinical improvement following Benadryl may be attributed to the antispasmodic effects of the drug rather than to its antihistamine properties.

We found Dibenzylene excellent in ameliorating the severity of cold sensitivity and Raynaud's syndrome. The vasodilating effect of Dibenzylene is the most likely basis for symptomatic relief. Serpasil, 0.25 mg. twice a day, has also been found helpful for the hypertension.

Therapeutic measures in general were discouraging. ACTH and cortisone did not produce qualitative changes in the serum globulin, nor did they show any dramatic effect on the clinical course. While there was some decrease in the amount of cryoglobulin following hormonal therapy to levels as low as 0.1%, it was not sufficient to prevent clinical manifestations. It may be noted that the lowest level obtained—.1 gm. cryoglobulin per 100 c.c. of blood—still represents several hundred times the amount considered markedly positive by Lerner and Watson.[22]

Recent studies on this patient (April, 1954) showed that, in spite of the cortisone therapy, the amount of cryoglobulin precipitated out of the serum was as high as ever obtained, namely, 18% by volumetric measurement (Cutler's sedimentation tube).

Nearly all cases of cryoglobulinemia reported in the literature [2, 1, 14, 22, 34, 33, 47] were associated with an underlying disease entity. The few instances where diagnosis was not fully established may very likely constitute early cases of myeloma. In one case (Barr) [2] of cryoglobulinemia without myeloma or leukemia the patient died as a result of nephritis. No primary condition was found.

The recent development of complicating nephritis and hypertension in our case may be of similar significance.

It has been observed that cases of myeloma complicated by cryoglobulinemia are more prone to develop severe uremic symptoms. It would seem likely that the generalized vascular changes also affecting the kidney parenchyma favor the precipitation of cryoglobulins as they do the deposition of other abnormal proteins (viz., amyloid, other myeloma globulins). The nephritis and hypertension in our case may therefore not be unrelated phenomena. The cryoglobulin plugs the capillaries of the kidney, resulting in parenchymatous impairment and subsequent hypertension. The sequence of events in this case suggests essential cryoglobulinemia unassociated with multiple myeloma or leukemia.

Summary

1. A case of cryoglobulinemia without the usually associated myeloma or leukemia is presented, with the suggestion that this type of cryoglobulinemia may represent a distinct clinical entity.

2. Observations on the clinical and laboratory features in this case are recorded, including electrophoresis and paper chromatography.

3. The effects of ergotamine tartrate, ACTH and cortisone, Priscoline and Dibenzylene on this patient are discussed.

4. The results of several allergic studies, including passive transfer, are summarized.

Summario in Interlingua

Es presentate un caso de cryoglobulinemia non associate con le normalmente coexistente morbo subjacente, como myeloma o leucemia. Nos face le proposition que iste typo de cryoglobulinemia representa possibilemente un distincte entitate clinic.

In un patiente feminin blanc de 45 annos de etate, non presentante signos de infection o neoplasma, le consideration de cryoglobulinemia esseva suggerite per le alte rapiditate del sedimentation, le stato gel-oide del sanguine, e le symptomas clinic de urticaria sub frigido e purpura.

Le sequente datos laboratorial esseva considerate como pertinente: (1) Le proportion de albumina a globulina esseva revertite; le globulina total esseva 6,6 g (includente 4,3 g cryoglobulina) e le albumina total esseva 4,1 g. (2) Esseva determinate le configuration electrophoretic de proteina seral e etiam le curva electrophoretic pro chromatographia a papiro. Iste ultime revelava un augmentate contento globulinic del sero, specialmente pro le fraction gamma. (3) Examines biomicroscopic del vasos conjunctive monstrava signos de constriction del arteriolas e fangositate e segmentation del columna de sanguine.

Le observationes clinic includeva le sequente: (1) Il occurreva repetite exacerbationes de manifestationes purpuric debite al administration de tartrato de ergotamina pro migraine. (2) ACTH e cortisona produceva un melioration clinic. Illos reduceva le contento cryoglobulinic del sero ab 4,3 a 0,1 g. (3) Durante le periodo ab duo annos post le establimento del diagnose (octobre 1953) usque al tempore del presente reporto (maio 1955), le patiente exhibiva le aspectos clinic de hypertension (220/110 mm Hg; previe registration: 110/70 mm Hg) con allargamento del corde, retinopathia, nephritis con edema, extense purpura e marmorisation del extremitates inferior con recurrente areas thrombotic circa le talos, e un anemia normocytic que requireva numerose transfusiones.

Doses de mantenentia de cortisona (25 a 37 mg per die, usate durante plus que un anno) pareva arrestar le progresso del morbo.

Es discutite le possibile nexo causal inter le declaration de nephritis e cryoglobulinemia.

Es summarisate studios allergic (includente le transferimento passive a urticaria sub frigido), le effecto benefic de Benadryl, le phenomeno de exhaustion de anticorpore, e le effectos therapeutic de Priscolina e Dibenzyleno.

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CARCINOID TUMORS OF THE STOMACH *

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CARCINOID tumors continue to evoke considerable interest, although they can no longer be considered medical rarities. Most commonly arising in the appendix, these tumors have been found originating in all parts of the gastrointestinal tract below the esophagus, including the mesentery and the gallbladder, and in a Meckel's diverticulum.[12] Extra-alimentary sites of origin reported include ovarian teratomas [12] and the bronchi.[20]

Of these many sites of origin, the great majority are found in either the appendix or the small intestine. Primary carcinoids of other organs still constitute a very uncommon finding. For this reason the following case of primary carcinoid of the stomach is reported. We believe it to be the twenty-sixth case of similar origin to be reported in the English literature. The largest collection of these tumors that we have found previously reported numbered 23.[12] The most recent review of the subject included 18.[8]

CASE REPORT

A 37 year old white woman was first seen by one of us (C. R. H.) on August 28, 1952, with a complaint of back pain which had been present for one week. This pain, which typically awakened her at night, was sharply localized to the infrascapular area. She had found relief by arising and maneuvering into rather bizarre postures similar to those described in patients with posterior penetrating ulcers. She had not tried food or antacids for relief.

Physical examination of the patient, a tall, slender woman, was normal except for bilateral cystic mastitis. There was no tenderness to abdominal palpation.

Laboratory examination, including complete blood count, urinalysis and sedimentation rate, was normal. No blood was found in three separate examinations of the stool with benzidine. Gastric analysis revealed a histamine-fast achlorhydria. There was gross blood in several of the specimens obtained during this analysis. Roentgenographic examination of the gastrointestinal tract showed a polypoid lesion in the fundus of the stomach (figure 1).

On September 22 the lesion was excised by one of us (J. L. S.). At operation a small (1 by 2.5 cm.) polypoid tumor was found to lie in the posterior wall of the stomach at about the junction of the upper and middle thirds and not far from the greater curvature. This was excised locally and was considered by the pathologist to be a fibroma. Later, permanent microscopic sections revealed it to be a carcinoid tumor. The report stated in part: "Gastric mucosa overlies and in one location is invaded by tumor which lies primarily in the submucosa. Some invasion of the stalk of the mass and the muscularis of the stomach is found" (figure 2). No enlarged lymph nodes were found.

In view of the true nature of the lesion, and because of the microscopic evidence of invasion, it was feared that a sufficiently wide resection had not been done. Accordingly, the patient was operated upon again on September 29 and a large, pie-shaped wedge of stomach was removed. No evidence of any additional tumor cells

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was found on microscopic examination of this segment, and no tumor-bearing nodes were found in the mesentery. The patient was discharged from the hospital October 10.

Subsequent follow-up studies through March, 1954, have revealed no clinical or roentgenographic evidence of recurrence of the tumor.

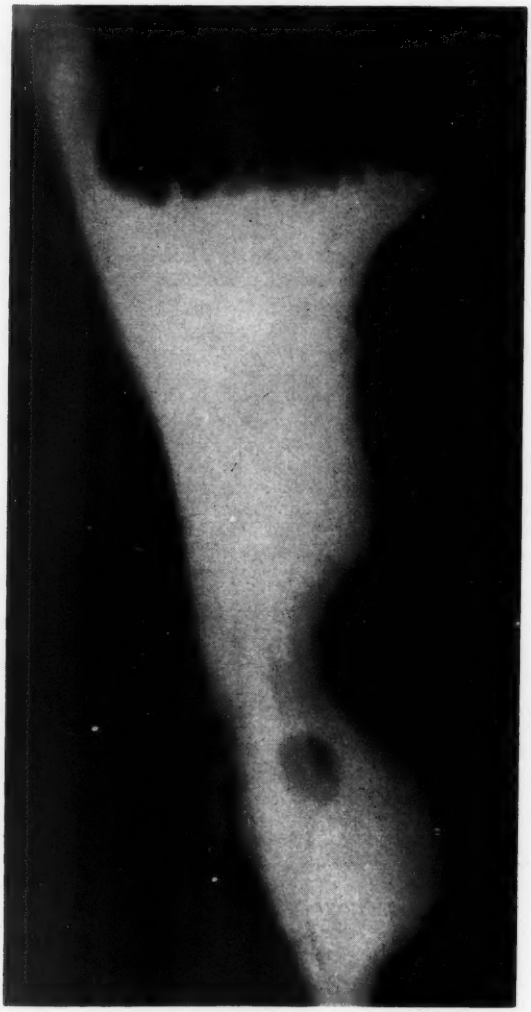

FIG. 1A. Roentgenographic appearance of the tumor in the stomach. The carcinoid is seen as a polyp in the fundus.

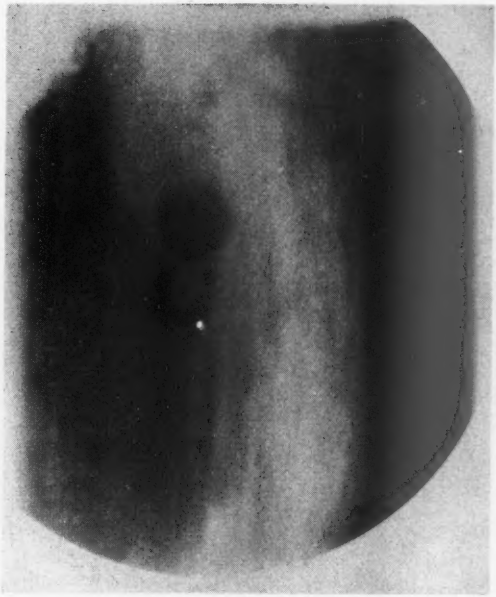

FIG. 1B. Roentgenographic appearance of the tumor in the stomach. The carcinoid is seen as a polyp in the fundus.

DISCUSSION

Many theories concerning the origin of carcinoid tumors have been advanced. That proposed by Masson is most generally accepted at present. He demonstrated the silver-staining characteristics common to the cells of this tumor and the chromaffin (Kulchitsky) cells of the gastrointestinal mucosa.[9] These silver-staining cells are presumed to be the histologic site of origin. From this staining characteristic has stemmed the name, argentaffinoma, which is frequently applied to them.

Whenever a carcinoid tumor is discovered clinically, the immediate concern must be with its possible malignancy. Originally considered benign tumors, carcinoids are now most commonly considered either definitely malignant or pre-malignant in nature.[1, 17] With occasional possible exceptions, the malignancy of any carcinoid tumor must be determined solely by the presence or absence of metastases. There is no specific change in the intrinsic appearance of the cells which has been correlated with a malignant course.[1, 8]

Comparisons have been made of the relative frequency of malignancy of these tumors in various sites of origin. It is generally agreed that carcinoids of the appendix are least likely to have metastasized.[13] There is much less agreement concerning those originating elsewhere. In an effort to establish some definite statistics specifically relating to carcinoids of the stomach, the 26 known

cases have been reviewed. Twelve of these 26 were found at autopsy and the other 14 as the result of surgical exploration.

Five of the 26 (19%) were considered malignant. One of the cases reported as benign included a microscopic report of a tumor-filled vein.[4] The

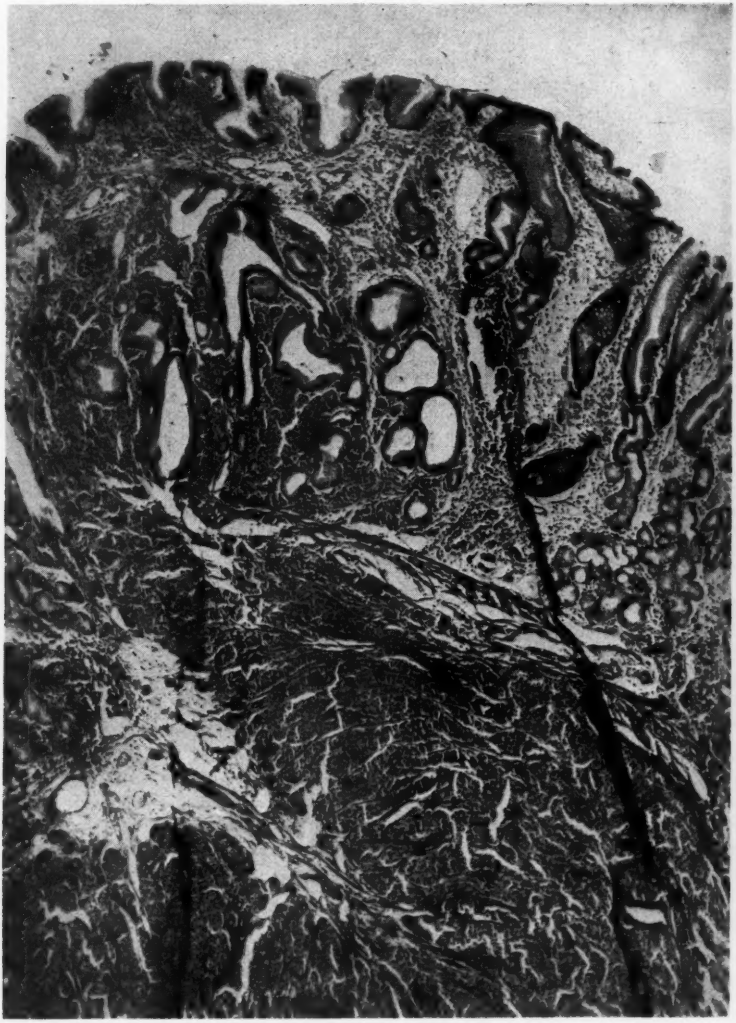

FIG. 2A. Photomicrograph, H & E stain, × 100. The tumor cells are seen throughout the submucosa and extending into the mucosa.

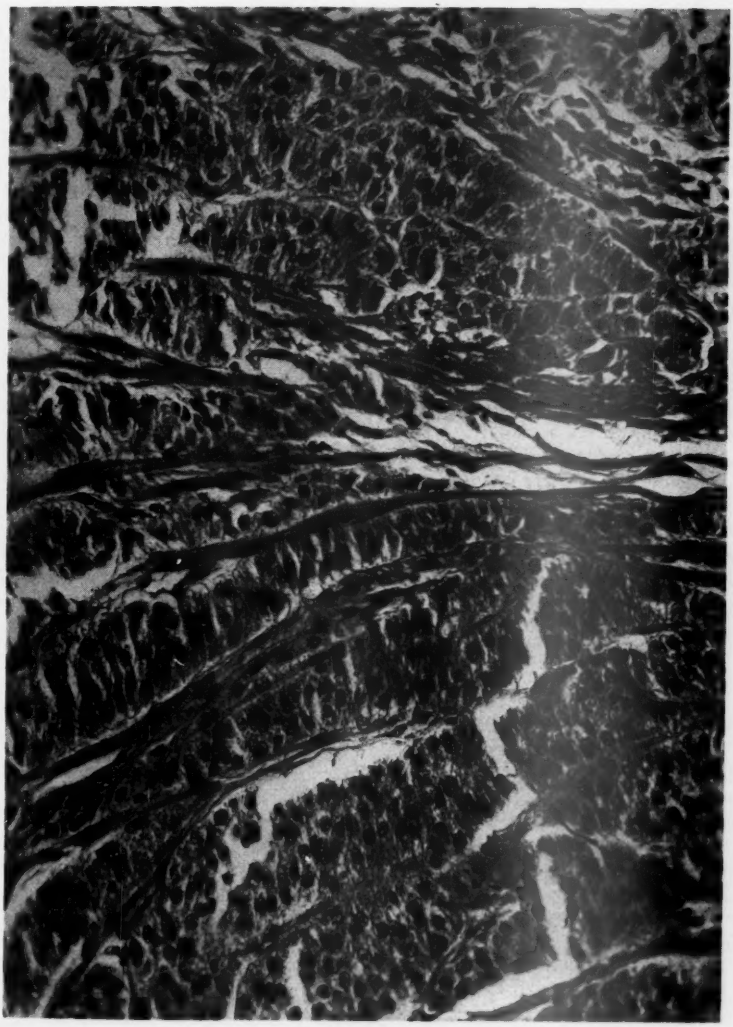

FIG. 2B. Photomicrograph, H & E stain, × 400. The higher magnification shows the "organoid" cell arrangement of a carcinoid. These cells took a silver impregnation stain.

possibility exists that this represents another malignant tumor. However, the presence or absence of malignancy was determined in this survey by the opinion of the author making the original report. Except for the autopsy cases, this opinion was based upon the original operative findings. No report was found of

recurrence or later metastasis of a carcinoid of the stomach thought to be benign. In the absence of follow-up reports, and because of the slow growth of these tumors and their metastases, a higher incidence of ultimate malignancy is possible.

This apparent incidence of malignancy of 19% is very similar to that reported for carcinoids occurring in many other sites. Of the 237 cases of small intestinal carcinoids collected by Ariel, metastases were found in 59 (24.9%).[1] Seven of 48 tumors (14.6%) in the rectum showed malignant invasion.[19] Sixteen of 42 non-appendiceal carcinoids (38%) reviewed at the Mallory Institute of Pathology were found to be malignant.[13]

Because of this significant incidence of malignancy, surgical removal of a carcinoid of the stomach is imperative. However, the exact procedure of choice is ill-defined. Procedures employed have been excision, gastric resection and total gastrectomy. This latter operation was performed on a patient erroneously thought to have carcinoma.[22] The authors of one comprehensive study advocate excision of any visible metastases because of their slow rate of progression.[13] As noted in this case report, it was determined to do a wide wedge excision of the stomach wall, with removal of the regional lymph nodes. This second operation seemed mandatory because the tumor cells were seen to extend into the line of original excision. In the absence of demonstrable metastases, it is hoped that this procedure will prove adequate.

In no case of carcinoid of the stomach was the correct histologic diagnosis made preoperatively or premortem. Of the 12 cases discovered at autopsy, clinical data are given in four. In these the finding of the carcinoid was considered incidental and unrelated to premortem symptomatology. This includes one patient with metastases to mesenteric lymph nodes.

No clinical data are available for one of the 14 cases in which the tumor was found at operation. Accordingly, evaluation is limited to 13 patients.

Exact correlation of symptoms and findings in these cases is difficult because not in all cases can these symptoms be specifically related to the carcinoid of the stomach. One patient had an associated gastric ulcer, for example.[6] Another noted no relief of symptoms following surgical removal of the tumor.[21] Previous reviews most often cite abdominal pain and gastrointestinal bleeding as presenting symptoms. Abdominal pain was present in eight of these 13 clinically discovered cases (62%). However, there was no consistent location or characteristic of the pain described, and it cannot be considered diagnostic. Gross gastrointestinal hemorrhage (melena or hematemesis) was reported in five of the 13 (38%). The other presenting complaints are listed in the accompanying table.

Of the four clinically discovered cases considered malignant, only one had abdominal pain.[18] The others complained of "vague indigestion,"[16] longstanding "digestive troubles"[10] and epigastric fullness and weight loss.[22]

Report of the results of roentgenographic examination of the stomach was found in seven of the cases. All but two were reported specifically as single or multiple polyps of the stomach. The two other opinions were "rounded—probably benign tumor masses"[5] and "gastric polyp or carcinoma."[7] One of these seven was malignant. No difference from the others was noted roentgenographically. Miller and Herrmann have reported a roentgenographic sign

which they consider suggestive of malignant carcinoid of the small intestine, and such a diagnosis was made preoperatively.[11] However, no such specificity can be found for carcinoid of the stomach. Certainly the majority will be seen as nonspecific polypoid lesions.

The results of a gastric analysis were reported in only four patients. Free acid was absent in three and present in one, in whom a concentration of 30 units was found. No information concerning the reaction of the achlorhydria to histamine is presented, with the exception of our case. One of these four cases was malignant, and that one had no free acid.[22] These are insufficient data from which to draw any conclusions.

The prognosis when a carcinoid of the stomach is removed is not definitely known. It is generally considered good, but this is presumptive. The reported

TABLE 1

Carcinoid of the Stomach
Summary of 26 Reported Cases

Presenting symptoms presumably caused by the tumor, and the incidence of their occurrence with gastrointestinal hemorrhage and malignancy.

Symptom	Number of Cases	Number with GI Bleeding	Number of Malignant
Tumors discovered at autopsy			
No clinical data	8		
No symptoms	4		1
Tumors discovered at operation			
Abdominal pain	8	5	1
Back pain	2	1	
Vague indigestion	1		1
Digestive troubles	1		1
Epigastric fullness and weight loss	1		1
Occasional nausea and vomiting	1		
No clinical data	1		
Total patients	26*	5*	5

* One patient had abdominal and back pain as well as a gastrointestinal hemorrhage. He also had a gastric ulcer.

postoperative data are entirely inadequate either to support or to refute this opinion. No statement is made concerning the result in eight of the operative cases. One patient died from the tumor and its metastases.[16] The other five patients who were operated upon were alive and apparently well at intervals varying from six months to two years. This latter group includes two malignant cases.

There seem to be two primary reasons for the presumptively good prognosis in these cases. One is the slow growth and metastasis of carcinoid tumors in sites of origin more common than the stomach.[1, 13] The second is based upon the results of a study of the apparent cause of death in the autopsy cases. In none was the carcinoid implicated. However, there was but one malignant tumor in this group, and the data in that case are insufficient to remove the carcinoid absolutely from suspicion.

We do not believe that any definite conclusions concerning prognosis can be drawn from a review of the results reported to date. It is likely that considerable time and many more cases with follow-up reports will be necessary. The ultimate incidence of recurrence or metastasis of the tumors thought benign at operation is unknown. The absence of such a report may speak only for the slow rate of growth.

Summary and Conclusions

This review of the available data from 26 reported cases of carcinoid of the stomach would seem to justify the following conclusions:

1. The apparent incidence of malignancy (19%) is similar to that reported for carcinoids arising in other extra-appendiceal sites.
2. Complete surgical excision of these tumors is indicated. The specific extent of such excision has not been defined.
3. No clinical symptom or laboratory finding can be considered specifically significant for the preoperative diagnosis of carcinoid of the stomach. Abdominal pain was most frequently encountered in this review.
4. Roentgenograms will most commonly demonstrate a benign-appearing polypoid lesion of the stomach.
5. The prognosis, following surgical excision, is presumed to be good.

Summario in Interlingua

Le examine roentgenographic revelava un lesion polypoide in le stomacho de un femina blanc de 32 annos de etate. Post excision chirurgic il esseva constatate que il se tractava de un tumor carcinoide. Un re-operation esseva interprendite, e un late e cuneiforme resection del stomacho esseva executate. Le examine del patiente 18 menses plus tarde revelava nulle recurrentia.

Iste caso representa le 26te primari tumor carcinoide del stomacho que nos ha potite discoperir. Le raritate de iste lesion (1) rendeva difficile le selection del optime procedimento chirurgic e (2) resultava in un prognose pauco definite. Pro resolver iste problemas nos interprendeva un revista del constatationes clinic e laboratorial e del procedimentos chirurgic e lor resultatos in le casos discoperite in le litteratura de lingua anglese.

Cinque del 26 tumores (19 pro cento) esseva considerate como maligne. Iste proportion es simile a illo reportate alterubi pro tumores carcinoide in sitos non-appendical. Super le base del datos disponibile, nulle specific procedimento chirurgic esseva identificabile o deducibile como procedimento de selection. On ha considerate le prognose como bon, sed isto solmente super un base presumptive. A causa del lente crescentia del cognoscite metastases, le reportate periodos de superviventia esseva inadequate.

Le plus frequente constatationes clinic e laboratorial esseva dolores abdominal de un typo non-specific (62 pro cento) e grossier hemorrhagia gastrointestinal (38 pro cento). Omne le publicate reportos roentgenologic esseva indicative de lesiones polypoide. In tres inter quatro reportate analyses gastric, le presentia de achlorhydria esseva constatate. In nulle caso esseva le diagnose solmente post-operative. Nulle datos clinic o laboratorial esseva de signification pro predicer le character maligne o benigne del lesion.

Tumor carcinoide del stomacho remane un del rar possibilitates in le diagnose differential de gastric lesiones polypoide. Al tempore presente iste diagnose pote esser effectuate solmente per medio de technicas microscopic. Le presente revista ha

resultate in nulle discoperta de datos clinic que esserea significative como base de un forma preoperative del diagnose. Le procedimento chirurgic a seliger remane indefinite e le prognose incerte.

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COEXISTENT MYELOGENOUS LEUKEMIA AND HODGKIN'S DISEASE*

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THE occurrence of myelogenous leukemia and Hodgkin's disease in the same individual has been noted but once before in the literature.[17] Such a case, clinically diagnosed as chronic myelogenous leukemia and subsequently found at autopsy to have Hodgkin's disease also, forms the basis of this report.

CASE REPORT

The patient, a 71 year old white woman, was admitted to this hospital on September 9, 1953, complaining of marked weakness, anorexia and considerable weight loss. Her present illness had begun insidiously about three years before admission. Until then she apparently had been well. Physical examination by the family physician at the onset of her complaints was said to have been unrevealing except for evidence of severe anemia. She was treated with an iron preparation for several months but failed to respond. During this time a definite enlargement of her spleen was discovered. A hematologic work-up at that time revealed a blood picture typical of chronic myelocytic leukemia (table 1). The patient was treated with a course of radiotherapy, triethylene melamine and Aminopterin, as well as blood transfusions. The disease remained quiescent until about two weeks prior to admission, when she developed a severe cough and respiratory distress and fever. A tentative diagnosis of leukemia and pneumonitis was made. Roentgenologically no evidence of pneumonia was found. The patient was treated with antibiotics and subsequently admitted to this hospital.

Physical examination on admission revealed a well developed 71 year old white female appearing chronically ill, debilitated and anemic. Her temperature was normal. The blood pressure was 110/70 mm. of Hg. Examination of her eyes, ears, nose and throat was within normal limits except for some pallor of the mucous membranes. The lungs were clear to percussion and auscultation. The heart sounds were of good quality and the rhythm was regular, with a systolic murmur present over the aortic area. On abdominal palpation a tremendously enlarged, firm spleen was felt extending down to the iliac crest. The liver edge was felt three finger-breadths below the right costal margin.

A hematologic study revealed the following: (a) peripheral blood: hemoglobin, 6.8 gm.; red blood count, 2.35 million; white blood count, 41,000, with a differential of 11 myeloblasts, 12 premyelocytes, 3 myelocytes, 4 staff forms, 39 polymorphonuclears, 12 basophils, occasional normoblasts and 70,000 platelets; (b) bone marrow aspiration (spinous process): good cellularity, with predominance of myeloblasts and myelocytes, relatively few normoblasts and no megakaryocytes seen on the smears; (c) splenic aspiration: a myeloblastosis with a slight erythroblastosis, an occasional megakaryocyte and many splenic pulp cells. The clinical impression was that of chronic myelogenous leukemia in the subacute phase, with osteosclerosis (radiotherapy, triethylene melamine) and extramedullary hematopoiesis in the spleen.[13, 14]

X-ray of the chest was reported as negative except for some widening of the thoracic aorta. The skull showed some hyperostosis frontalis interna, and a skeletal

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survey revealed some arthritis of the spine. No destructive lesions of the bone were discovered.

Laboratory Data: Blood chemistries were essentially normal except for a total cholesterol of 118 mg.%, with 65% cholesterol esters, a slightly increased alkaline phosphatase of 15.4 K.A. units, a lowered total protein of 5.1 gm.% with a normal A/G ratio, a urea nitrogen of 32.7 mg.%, a uric acid of 4.65 mg.%, and a cephalin flocculation of 2 plus. Urinalysis was repeatedly negative except for occasional albuminuria of 1 plus.

TABLE 1

Peripheral Blood and Bone Marrow Aspiration (15)
June 11, 1951

Blood Count		Bone Marrow		
			Per Cent	Normal
Hemoglobin	9.5 gm. (60%)	Nucleated cells		1,000,000
Red cells	3,170,000	Megakaryocytes		44
White cells	226,000			
Platelets	610,000	Myeloblasts	2%	0–3
		Progranulocytes		
Myeloblasts	3%	(Promyelocytes)	1%	0–4
Progranulocytes	9%	Myelocytes		
Myelocytes neut.	25%	Neutrophilic	41%	10–30
Metamyelocytes	10%	Eosinophilic	6%	0–4
		Basophilic		0–1
Polys. band	23%	Metamyelocytes	6%	3–10
Polys. seg.	22%			
Polys. eos.	2%	Band cells	19%	
Polys. bas.	5%	Segmented	14%	
		Neutrophilic		10–30
Lymphocytes	—	Eosinophilic	6%	0–4
Monocytes	1%	Basophilic	2%	0–0
Hematocrit	35%	Plasmacytes		0–3
		Lymphocytes	3%	1–15
Normoblasts	1 per 100 WBC	Hematogones		0–10
		Reticulum		0–2
Reticulocytes	1.0%	Rubriblasts		0–0
		Proerythroblasts		0–1
		Rubricytes (erythroblasts)		2–15
		Metarubricytes (normoblasts)		7–30
		Megakaryoblasts	4%	
		Promegakaryocytes	62%	
		Megakaryocytes	34%	
		Platelet-forming	50%	

Course in Hospital: The patient received several blood transfusions, and on September 22 was started on a course of Myleran. Eighteen days after the beginning of treatment the white blood count declined to 50% of the pretreatment level. There was a depression of the hemoglobin to 7.0 gm. and the platelets to 28,000. The spleen remained unchanged. Twenty-seven days after treatment the patient developed a severe diarrhea, and Myleran was discontinued. At this time there had been a further decrease of the white blood count to 5,600 and the platelets to 18,000. Despite repeated transfusions and supportive therapy the patient's condition deteriorated gradually and she died on November 5, 1953. During the entire course of hospitalization her temperature ranged from 100° to 102° F. Her final blood count

on November 3 (figure 4) was as follows: hemoglobin, 7.6 gm.; red blood count, 2.18 million; white blood count, 56,000, with a differential count of 73 myeloblasts, 6 myelocytes, 6 polymorphonuclears, 9 staff forms and 6 lymphocytes.

Autopsy Findings (Dr. Bruno W. Volk, Pathologist):

General Description: The body was that of a well developed, obese white female measuring 5 feet 3 inches in length and weighing about 160 pounds. The skin, conjunctivae and the visible mucous membranes were pale. Petechial hemorrhages of the tongue and upper extremities, as well as a large ecchymosis in the left cubital fossa, were present. One plus pitting edema of both ankles was noticeable.

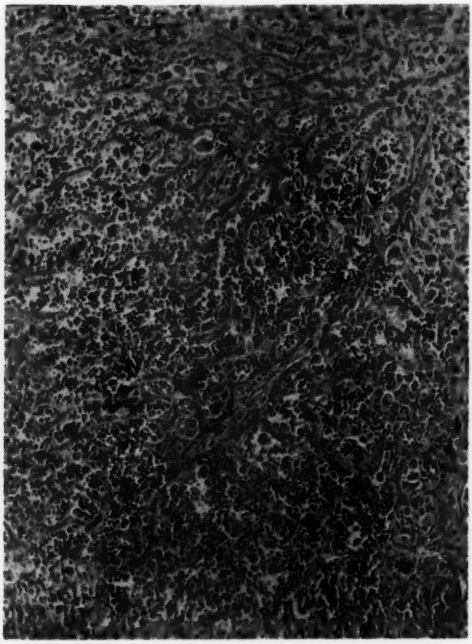

FIG. 1. Liver. Hodgkin's sarcoma infiltrating the liver with pleomorphic tissue, including numerous Reed-Sternberg cells. Marked compression of liver cords. H. & E. stain. 57 ×.

Gross Examination: Heart: Weight, 300 gm. Except for moderate sclerosis of the left descending branch of the coronary arteries there were no significant abnormalities.

Liver: Weight, 3,300 gm. The consistency was firm. On the cut surface the architecture was somewhat blurred. The color was light brown, mottled, with pinhead-sized grayish areas. Scattered, minute hemorrhages were noticeable.

Spleen: Weight, 3,300 gm. The capsule was slate gray, smooth and tense. On sectioning the pulp was a dark purplish gray, mottled with pink-gray areas measuring up to 3 mm. in diameter. Noticeable were several wedge-shaped, subcapsular, yellow-gray soft areas which measured from 0.5 to 1.5 gm. in the longest diameter.

Gastrointestinal tract: There were scattered submucous hemorrhages in the fundus of the stomach as well as throughout the small and large bowel, but most marked in the jejunum and cecum. The intestinal contents consisted of a semi-liquid, sanguineous material.

Bone marrow (left femur): The bone marrow was gelatinous in consistency and gray in color.

Brain: Weight, 1,080 gm. There were several small, yellowish, discrete plaques which measured about 3 mm. in the cerebral falx. The leptomeninges showed focal and linear areas of diffuse hemorrhage. Otherwise no gross changes of the brain were noticeable.

On gross examination the remaining organs showed no significant abnormalities.

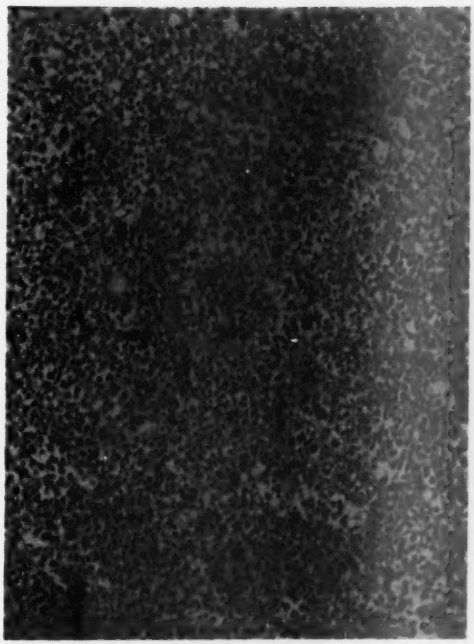

FIG. 2. Bone marrow. Completely replaced by Hodgkin's sarcoma. H. & E. stain. 57 ×.

Microscopic Examination: Liver (figure 1): The architecture was severely distorted. There was extensive dissociation of the liver cords. These were in most instances compressed by markedly distended sinusoids, which were densely filled with a pleomorphic cellular tissue with no distinct architecture. It consisted of multinucleated or binucleated giant cells, as well as lymphocytes, fibroblasts and plasma cells. The multinucleated cells, particularly the binucleated variety, resembled Sternberg-Reed cells and contained hyperchromatic, somewhat pyknotic nuclei. The portal fields were occasionally widened and showed scattered infiltration with round cells.

Spleen: The architecture was markedly distorted. The lymph follicles had

disappeared. The sinuses were conspicuously distended and contained a pleomorphic tissue similar to that described in the liver. The pulp cords were infiltrated by similar cells. Several areas showed extensive coagulation necrosis. Numerous small hemorrhages were noticed throughout the splenic tissue.

Cerebral falx: Sections through the abovementioned yellowish plaques of the cerebral falx disclosed a similar pleomorphic tumor tissue.

Bone marrow (figures 2 and 3): Sections from the bone marrow of the left femur showed almost complete replacement by the same pleomorphic tissue described above. Here and there areas of fibrosis and small foci of necrosis were scattered throughout the sections. In a section from the spinous process of the fourth lumbar vertebra the bone marrow was hyperplastic and consisted of white blood cells, predominantly of the myelocytic and, to a lesser degree, of the myeloblastic variety.

Kidneys: Weight, 300 gm. The medullae and to a lesser degree the cortices of both kidneys showed infiltration by tumor tissue as described above. Otherwise no significant changes were noted.

Retroperitoneal lymph glands: Sections through some of the retroperitoneal lymph glands showed extensive replacement of the parenchyma by the same neoplastic tissue observed in the other organs.

Anatomic Diagnosis: (1) Hodgkin's sarcoma involving the bone marrow, spleen, liver, the retroperitoneal lymph glands, the adrenals, kidneys and the cerebral falx. (2) Chronic myelogenous leukemia. (3) Splenomegaly. (4) Hepatomegaly. (5) Submucous hemorrhages of the gastrointestinal tract. (6) Bilateral pyelonephritis,

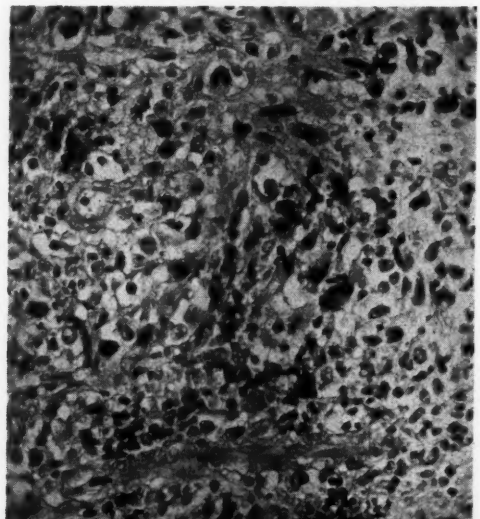

FIG. 3. Bone marrow. Hodgkin's sarcoma with areas of fibrosis. H. & E. stain. 380×.

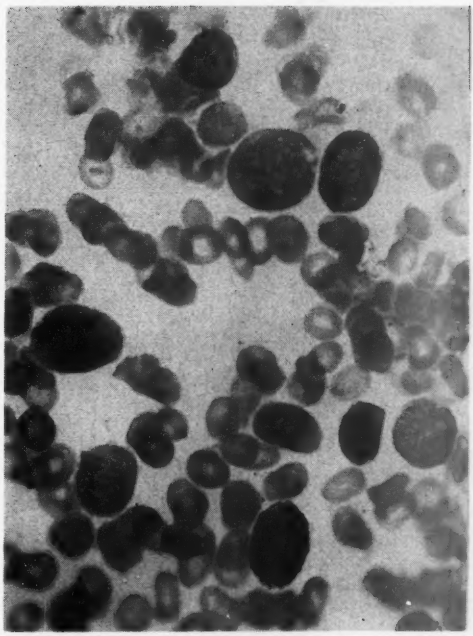

FIG. 4. Peripheral blood. Smear showing myelocytes and myeloblasts. Wright's stain. Oil immersion. 1250 ×.

chronic, mild. (7) Trigonitis, mild. (8) Pulmonary edema. (9) Ascites. (10) Uterine polyp. (11) Polyp of the cecum. (12) Decubiti, both heels.

DISCUSSION

Leukemia and carcinoma in the same individual [1, 12, 20] have been noted in a number of instances. With regard to lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoblastoma, Hodgkin's disease and multiple myeloma, much has been said concerning their relation to and combination with lymphatic leukemia.[5, 6, 7, 8, 16, 18, 19] Not only may the clinical pictures of these disorders shade from one condition to the other, so that a whole spectrum can be described, but also different sections of the same gland or sections of different glands may show in a given case histologic patterns ranging from that of Hodgkin's disease to that of reticulum cell sarcoma and lymphosarcoma, while the histologic pattern of lymphosarcoma is indistinguishable from that of lymphocytic leukemia.[3, 8, 20]

Monocytic leukemia occurring with Hodgkin's disease was reported by Craver.[2]

Skworzoff [17] in a critical review of the literature presented the unique case described as "acute myeloid leukemia which responded well to irradiation before the presence of Hodgkin's disease was noted." The patient, an eight year old

girl, presented hepatomegaly, splenomegaly, severe anemia and a white blood count of 360,000. Fabian's case [4] of Hodgkin's disease and chloroleukemia had blood examinations taken only post mortem. The leukocytosis of 22,000 with 24 myelocytes and no myeloblasts which was found was attributed by Skworzoff to the changes of the agonal period prior to death.

Our case report is that of a 71 year old white woman who was diagnosed as chronic myelogenous leukemia two years before entering the hospital (chart 1). Prior to admission she had had a course of radiotherapy followed by a course of Aminopterin and then by a course of triethylene melamine. After admission she received several blood transfusions and was started on a course of Myleran, which soon had to be discontinued because of the severe diarrhea. The patient died after a stay of two months in the hospital.

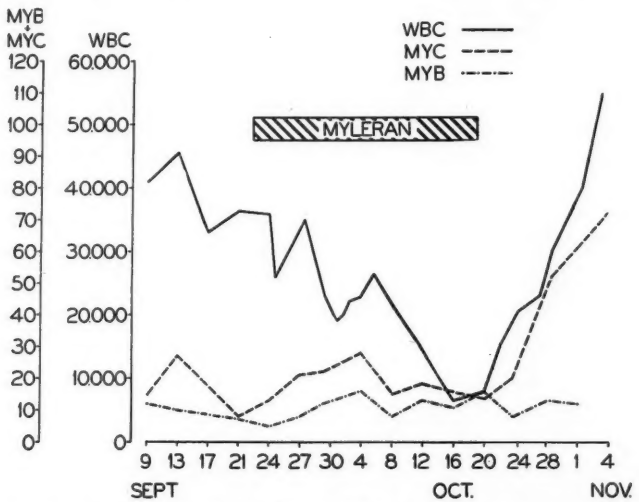

CHART 1. Variation of white blood cells (W.B.C.), myelocytes (Myc.) and myeloblasts (Myb.) during the patient's stay at the hospital.

The question of Hodgkin's disease and leukemoid reaction in this case was considered and the arbitrary criteria of Hill and Duncan [9] were reviewed. These authors state that for the myeloid type of leukemia a white blood count of over 50,000, with the presence of more than 2% of myeloblasts in the peripheral blood, is needed. Our case originally had 226,000, and in spite of the courses of radiotherapy, triethylene melamine, Aminopterin and Myleran, showed a leukocytosis which at times exceeded 50,000 and always showed many myeloblasts and myelocytes (chart 1). Furthermore, on the basis of Jackson and Parker's criterion that Hodgkin's sarcoma rarely lasts more than two years,[10] our case showed a leukocytosis of leukemic proportions long before Hodgkin's sarcoma appeared and was not influenced by it. Several bone marrow aspirations revealed the leukemic picture.

A review of the splenic aspiration slides, in view of the autopsy findings, revealed the myeloblasts, myelocytes, erythroblastosis and splenic pulp cells. A few of the "megakaryocytes" were Sternberg-Reed cells and could easily have been overlooked and misinterpreted. Terminally, the patient showed a myeloblastosis in the peripheral blood, and at necropsy this myeloblastosis was seen in a section of bone marrow from a vertebra. Hodgkin's sarcoma was seen in sections from most of the organs.

Summary

1. A case is reported of myelogenous leukemia which, after treatment with radiotherapy, triethylene melamine, Aminopterin and Myleran, terminated as an acute myeloblastic leukemia, and the patient was found at autopsy to have Hodgkin's disease.
2. A review of the literature is presented.

Summario in Interlingua

Es presentate le caso de un femina blanc de 71 annos de etate pro qui un diagnose de chronic leucemia myelogene habeva essite establite duo annos ante su admission al hospital. Illa habeva recipite un curso de radiotherapia, sequite per un curso de Aminopterina e postea per un curso de triethylenemelamina.

Al hospital le patiente recipeva plure transfusiones de sanguine e un curso de Mylerano que tosto debeva esser interrumpite a causa del occurrentia de sever diarrhea. Le patiente moriva post duo menses al hospital.

Examines terminal revelava le presentia de myeloblastosis in le sanguine peripheric. Al autopsia iste myeloblastosis esseva notate in un section de medulla ossee ab un vertebra. Sarcoma de Hodgkin esseva notate in sectiones ab le majoritate del organos.

Un revista critic del litteratura monstrava que usque nunc le coexistentia de leucemia myelogene e morbo de Hodgkin in le mesme patiente ha essite observate non plus que un sol vice. Iste caso esseva reportate per Skworzoff. Il se tractava de un puera de 5 annos de etate con hepatomegalia, splenomegalia, sever anemia, e un conto de leucocytos de 360.000. Illa respondeva ben a irradiation ante que le presentia de morbo de Hodgkin esseva notate.

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SPONTANEOUS PNEUMOTHORAX COMPLICATING PNEUMOPERITONEUM THERAPY: A REVIEW AND REPORT OF A CASE*

By Morton Shapiro, M.D., *Long Beach, California*

For more than two decades the use of artificial pneumoperitoneum in the treatment of pulmonary tuberculosis has been a well recognized procedure. This form of therapy has also found wide acceptance in the management of severe cases of pulmonary emphysema. Therefore, it is not surprising that increasing reports of complications of this therapy should find their way into the literature. Stein [1] described over 40 such complications occurring in 5 to 6% of all patients who received artificial pneumoperitoneum, and among these, spontaneous pneumothorax was listed as of relatively rare occurrence. A review of the literaature, however, reveals that this entity has been reported with increasing frequency in the past several years.

Banyai and Jurgens [2] and Banyai [3] differentiated two types of pneumothorax following pneumoperitoneum. The accidental type was frequently encountered when pneumoperitoneum was administered via the intercostal route and air entered the intrapleural space rather than the peritoneal cavity. Since this approach has been abandoned this type of pneumothorax rarely ever occurs. With

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the present method of introducing air via the para-umbilical route the possibility of faulty technic has been eliminated. The second type of pneumothorax which occurs in association with pneumoperitoneum is the spontaneous variety, and is due to the passage of air from the peritoneal cavity through the diaphragm into the pleural cavity. It is this latter group which forms the subject of this report.

Since the first case was described in 1939, only 36 cases have been reported in the world literature. Twelve additional cases were listed by a group of California chest physicians in answer to a questionnaire submitted by Ross and Farber.[4] As a result of personal communications with five physicians in the St. Louis area, four cases were mentioned by Lawton.[5] Breathnach[6] collected four cases from the major sanatoria and chest hospitals in Ireland. Guillaudeu and Stewart[7] found three cases of right-sided pneumothorax while reviewing the chest films of 500 patients receiving pneumoperitoneum.

The first case described by Mellies[8] occurred in a 16 year old female who developed a spontaneous pneumothorax three weeks after the induction of pneumoperitoneum. On the roentgenogram, both pleural and peritoneal fluid was noted, and by changing the position of the patient the presence of a free communication of fluid through the diaphragm was established. Shortly thereafter, Banyai and Jurgens[2] reported the second case after a routine pneumoperitoneum refill caused chest pain and dyspnea, and a chest film revealed right-sided pneumothorax with simultaneous decrease in sub-diaphragmatic air. In 1943 Smith[9] described a fatal case of bilateral pneumothorax following induction of pneumoperitoneum. Simmonds[10] reported nine cases of air embolism and pneumomediastinum (mediastinal emphysema) complicating pneumoperitoneum therapy, and among the latter an asymptomatic right-sided spontaneous pneumothorax was found on roentgenogram. In Sita Lumsden's[11] case an immediate increase of air in the right pleural cavity following each pneumoperitoneum refill was noted. Belbenoit[12] has recently reported a similar case occurring immediately after the induction of pneumoperitoneum, but the resulting pneumothorax was seen on the left side.

The first fatal case in this country was described by Yannitelli[13] in a 16 year old female who developed right-sided spontaneous pneumothorax after 10 months of pneumoperitoneum therapy. Two bleblike shadows projecting above the middle of the right leaf of the diaphragm were noted on the roentgenogram following the leakage of air. Five months after pneumoperitoneum refills had been resumed, however, the patient suddenly died. Autopsy disclosed a small opening on the peritoneal surface of the diaphragm which communicated with a bleb on the pleural surface. Laird[14] had previously reported the presence of similar blebs on the upper surface of the diaphragm during thoracoscopy in four patients who were receiving concurrent pneumothorax and pneumoperitoneum.

In recent reports the presence of demonstrable bleb formation has assumed a role of increasing significance. Sitá Lumsden observed two blebs at thoracoscopy. On the roentgenogram Street[15] noticed a bleb over the right leaf of the diaphragm, and three weeks later air was found in the right pleural cavity. Lawton[5] described a thin-walled bleb above the liver two and a half months prior to pneumothorax, while in Miller's[16] case a bulla was visualized after the diaphragm had ruptured. Ross and Farber[4] suggested that the pleural blebs might represent a herniation of peritoneum through a diaphragmatic defect, and

that a sufficient increase in intra-abdominal pressure could rupture these air sacs. Two of their three cases developed such an increase in pressure by straining at stool and lifting heavy objects. Oritt and Hyde [17] reported the surgical removal of a bleb prior to rupture, and on examination the specimen was found to be an eventration of peritoneum through the diaphragm. Recently four cases of air-

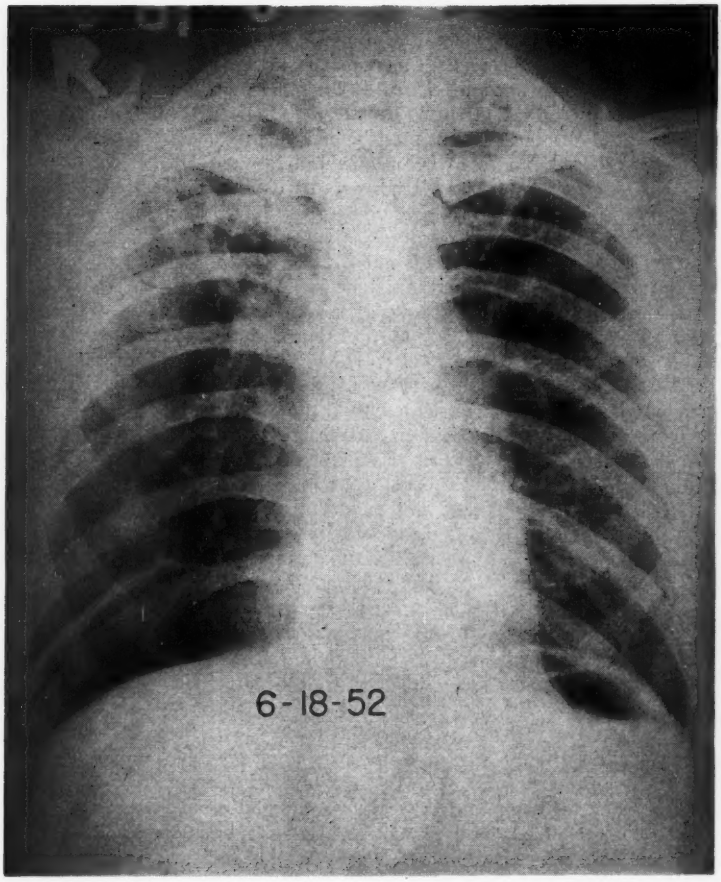

FIG. 1. Chest roentgenogram taken three weeks after induction of pneumoperitoneum. Note abnormal thinning of medial half of right dome of diaphragm.

filled sacs arising from the diaphragm were described and designated as diaphragmatic pneumatoceles. Three of these ruptured and produced right-sided pneumothorax.[7]

It has been definitely established that a rupture of the diaphragm can occur in these cases. Wynn-Williams [18] reported two rounded, air-containing bullae

prior to the pneumothorax, and subsequent thoracoscopy revealed a bright red area on the diaphragm. Repa and Jacobson [19] described a small slit in the diaphragm which they felt represented the rupture of a diaphragmatic cyst, similar to one seen at thoracoscopy. Two black areas in the pleural covering of the tendon of the diaphragm were present in the case of Spencer Jones and

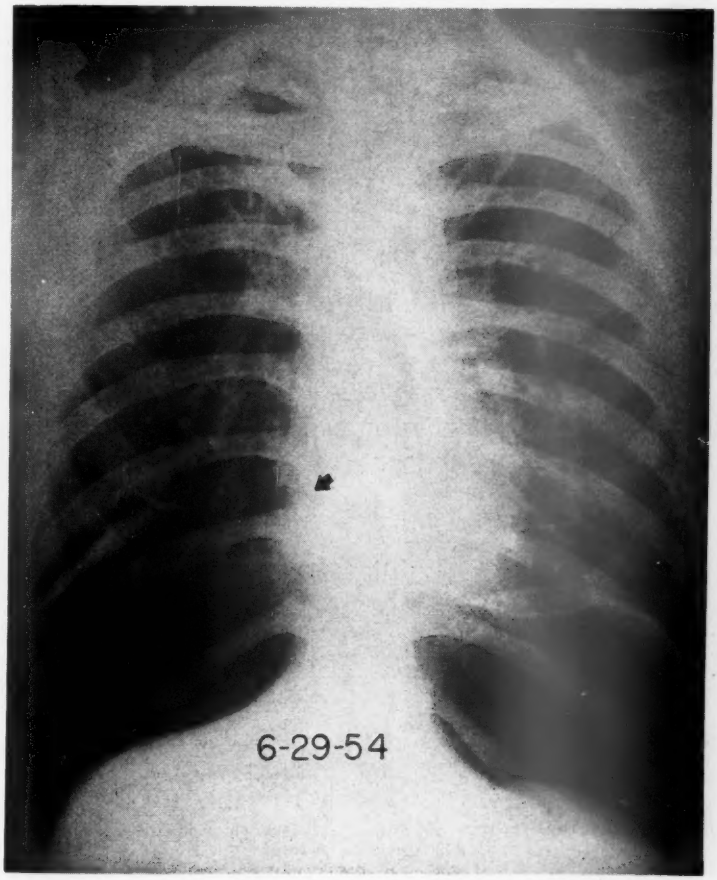

FIG. 2. Chest roentgenogram three weeks prior to pneumothorax. Thinning of right dome of diaphragm still present.

Yuill,[20] while Miller observed pleural deposits of fibrin, adhesions and blood in the right costophrenic angle following the air leak. Most authors are of the opinion that a congenital weakness or defect in the diaphragm is asymptomatic until the protection afforded by the liver is removed by the intervening pneumoperitoneum, and then air leakage may occur. This is also the probable ex-

planation of why almost all cases have occurred on the right side. Riegel [21] and Belbenoit [12] reported left-sided cases immediately following the induction of pneumoperitoneum, and in 1954 the first two cases of left-sided spontaneous pneumothorax arising during the course of pneumoperitoneum therapy were described by Howells.[22]

Most reports of this complication have appeared in the literature dealing exclusively with diseases of the chest and therefore reach only a small segment of

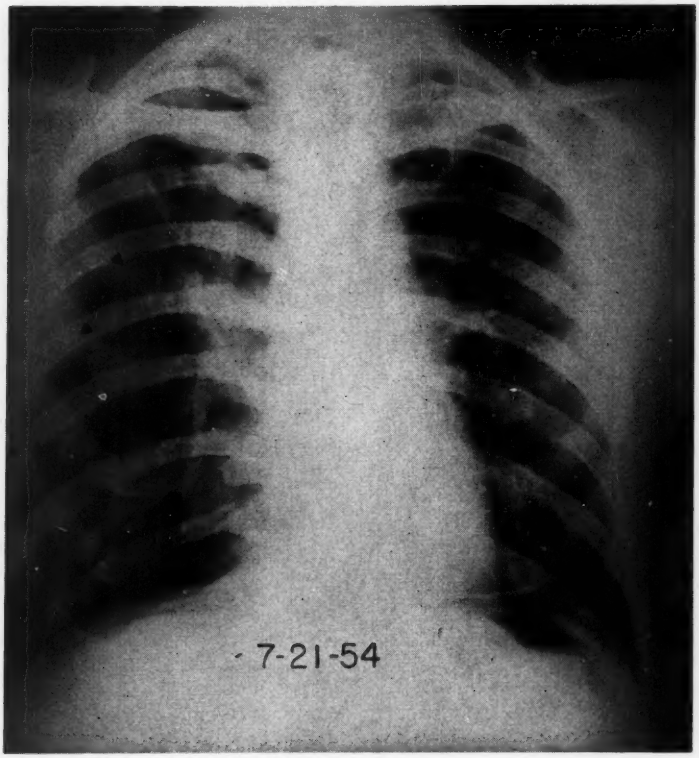

FIG. 3. Five days after onset of pain. Note right-sided pneumothorax and disappearance of subdiaphragmatic air.

the medical profession. In order to stimulate more widespread interest and awareness of this somewhat unusual condition, the following case is presented.

CASE REPORT

A 34 year old Spanish-American male developed a left pleural effusion in 1942. Sputum cultures were positive for *Mycobacterium tuberculosis* and the patient was treated for several months with bed-rest. In January, 1947, he was again hospitalized

and remained at bed-rest for 15 months. In May, 1952, a gastric culture was positive for *M. tuberculosis,* and on his admission to hospital the roentgenogram showed an increase in infiltration at the right apex with visible cavitation. On May, 25, 1952, pneumoperitoneum was induced (figure 1), and streptomycin, 1 gm. twice weekly, and para-aminosalicylic acid, 12 gm. daily, were begun. Pneumoperitoneum refills of 800 c.c. of air were given at weekly intervals, with average pressures ranging from plus 12 to plus 18. Treatment was continued without interruption. In June, 1953,

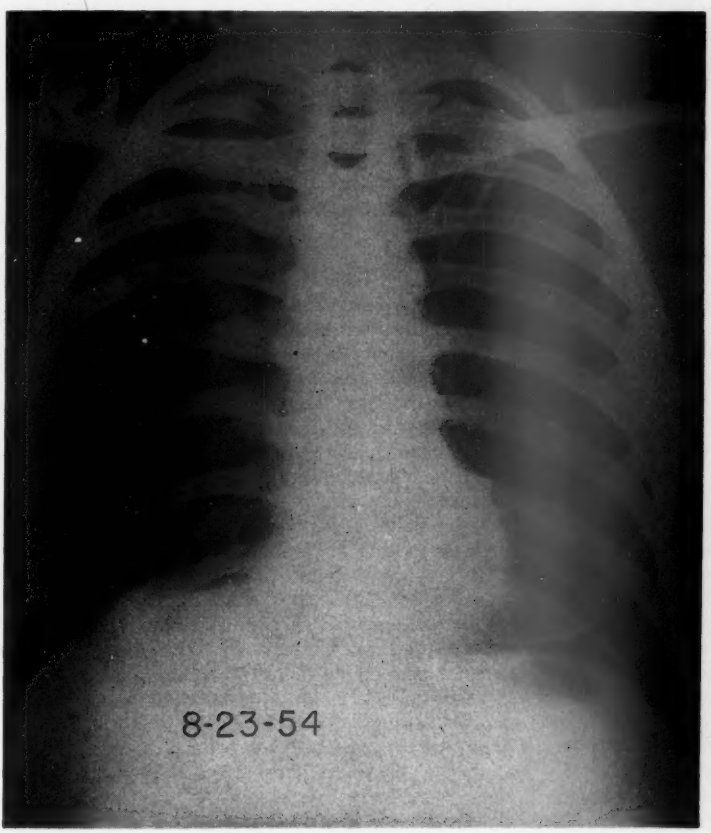

FIG. 4. Complete reëxpansion of right lung now present.

resectional surgery was recommended but the patient refused. On January 7, 1954, after all gastric cultures for one year had been reported as negative for *M. tuberculosis,* the patient was discharged from hospital and treatment was continued as an ambulatory outpatient. Chemotherapy and weekly refills of 800 c.c. of air were given, and the intra-abdominal pressures continued to range from plus 12 to plus 16. A chest roentgenogram on June 29, 1954, was unchanged from previous films (figure 2).

On the morning of July 16, 1954, two days after the last refill, while straining

at stool, he suddenly experienced a "gurgling" pain radiating from the epigastrium to the right side of the chest. This was followed by slight shortness of breath which persisted for several days. On returning for his regular refill on July 21, 1954, right-sided pneumothorax was seen on the roentgenogram (figure 3). At this time the patient was asymptomatic (temperature, 99.4° F.; pulse, 78; respirations, 20). On July 26, 1954, he was re-admitted to hospital.

Physical examination was essentially negative except for a decrease in breath sounds in the right chest posteriorly. The patient continued to remain asymptomatic, and by August 23, 1954, the right lung had completely reëxpanded (figure 4). No further pneumoperitoneum was given and the patient was again discharged to outpatient care.

Discussion

The diagnosis of spontaneous pneumothorax complicating artificial pneumoperitoneum can be made only when partial or complete loss of intraperitoneal air is demonstrated with the simultaneous appearance of air in the pleural cavity. The exact method by which this leakage of air across the diaphragm occurs, however, is still obscure. Banyai and Jurgens [2] suggested that the peritoneal air passed through the hiatuses of the diaphragm along the connective tissue sheaths of the esophagus and great vessels into the mediastinum, where the increasing tension of air ruptured the pleural membrane. Simmonds [10] also favored this theory of mediastinal emphysema preceding rupture into the pleural cavity. However, these authors offered very little evidence of mediastinal emphysema in the signs and symptoms recorded in their cases. This theory also failed to explain why almost all the cases occurred on the right side, whereas in the presence of mediastinal emphysema Dickie [23] noted that the complicating spontaneous pneumothorax occurred with equal frequency on both sides.

In recent years, most observers have concluded that air from the pneumoperitoneum passes into the pleural cavity through some defect in the diaphragm. These defects may be congenital, traumatic, degenerative or inflammatory in origin. Since the first two appear to be involved most frequently, it might be of value to review some of the salient features of the origin, development and structure of the diaphragm.

According to Meyer,[24] the communication between the pleural and peritoneal cavities closes in the third month of intra-uterine life. The septum transversum and the fused ventral mesentery give rise to the anterior, lateral and central portions of the diaphragm, while fusion of the dorsal mesentery and mesoderm with the pleuroperitoneal membrane forms the posterior, lateral and central portions. The pleuroperitoneal membrane is derived from the pulmonary ridge and grows ventrally. It closes the remaining opening in the diaphragm, the pleuroperitoneal hiatus, by fusion with the septum transversum and thus the lateral portion of the diaphragm is formed.

If there is improper deposition of mesoderm at the points of union, or if proper fusion fails to occur, then congenital weak points in the diaphragm may result. These are:

1. The pleuroperitoneal hiatus or foramen of Bochdalek, which is situated dorsolaterally.
2. The outer crus.
3. The esophageal hiatus.

The diaphragm is composed of three parts inserting into a central tendon. These parts, according to their point of origin are:

a. The sternal portion, arising from the xiphoid process.
b. The costal portion from the six lower ribs.
c. The lumbar portion arising posteriorly from the crura and the two lumbocostal arches.

Failure of fusion of the lumbar and costal portions results in a persistent hiatus, i.e., the pleuroperitoneal hiatus or foramen of Bochdalek. Failure of fusion of the sternal and costal portions results in an opening on either side of the xiphoid process which is covered by pleura above and peritoneum below. These openings are the foramina of Morgagni or Larrey's spaces, and transmit the deep epigastric vessels.

Even in the normal adult the muscle fibers of the outer crura and the last muscular portion of the costal part of the diaphragm may be separated by a triangular space which is filled in by a thin layer of connective tissue covered above by pleura and below by peritoneum. This area is protected by the liver and the fatty tissue surrounding the adrenal and kidney on the right, which probably explains why 95% of all diaphragmatic herniae occur on the left.

Although the congenital defects of the diaphragm are more common on the left side, almost all reports of spontaneous pneumothorax complicating pneumoperitoneum have been reported on the right. It has been suggested that the support normally given to the diaphragm by the liver is removed by the pneumoperitoneum pushing these two organs apart, and that any further increase in intra-abdominal pressure might be the deciding factor in causing an air leak into the pleural cavity. Such precipitating mechanisms as straining at stool, coughing, lifting, bending and attacks of vomiting have been mentioned.

A review of table 1 shows that cases may be divided into two types. In the first type are those cases which develop immediately after the induction of pneumoperitoneum. Of the 36 documented cases in the world literature, five fall into this category. In Smith's case postmortem examination revealed a number of small holes in the diaphragm connecting the pleural and peritoneal cavities, while others have felt that their cases were due to a patent pleuroperitoneal canal.[11, 12] Therefore, the immediate type is apparently due to a congenital defect in the diaphragm. The second type includes those in whom the pneumothorax has occurred at varying time intervals after the induction, i.e., from days to many months. These cases are caused by a tear or rupture of the diaphragm, and from table 1 it will be seen that the great majority fall into this group. To explain the pathogenesis, it is assumed that a congenital weakness has always existed in the diaphragm. The constant prolonged pneumoperitoneal pressure then produces further weakening and stretching until a final further slight increase in the intra-abdominal pressure is sufficient to cause a tear in this weakened area. During the phase of progressive weakening the bleb formation noted by various authors occurs and precedes the stage of rupture. These blebs appear as air-containing bullae and have been seen both on the roentgenogram and by thoracoscopy. Of the 36 cases reviewed, 10 showed this characteristic finding on x-ray, either above or below the leaf of the diaphragm. Hallam Cope [4] observed a large diaphragmatic bleb which varied in size with

TABLE 1

Available Data in All Reported Cases of Spontaneous Pneumothorax Complicating Pneumoperitoneum

Case No.	Author	Age	Sex	Duration of PNP	Average PNP Press.	Precipitating Factors	Symptoms at Onset	Time after Refill	Aver. Amt. of Refill	Bleb Formation on X-Ray	Pleural Aspiration Performed	PNP Cont. after PNX	Recurrence of PNX	Phrenic Interruption	Time of PNX after Phrenic	Remarks
1.	Mellies[8]	16	F	21 days	+6 +8	×	Chills, fever, tachycardia, abdominal pain	Next day	300–500 c.c.	×	×	×	×	Right phrenic	4½ months	After PNX, change of position of patient resulted in change of position of two fluid levels.
2.	Banyai and Jurgens[2]	53	M	12 months	—	×	Right chest pain, dyspnea	1½ hours	500–1,500	×	Yes	Yes	×	×	×	—
3.	Smith[9]	—	F	Same day	—	—	Chest pain, dyspnea	—	—	×	—	—	—	—	—	Patient collapsed and died after induction. Autopsy revealed bilateral PNX.
4.	Simmonds[10]	29	F	8 months	+10	—	Right chest pain, severe dyspnea	—	—	—	Yes	—	—	—	—	Symptoms occurred several days after PNX was seen on x-ray.
5.	Sita Lumsden[11]	38	F	Same day	+5	×	Shortness of breath	Immediately	1,000	×	Yes	Yes	Yes	Yes	2 weeks	Repeated test PNP refills always produced immediate PNX. At thoracoscopy, 2 subpleural air bubbles were seen.
6.	Yannitelli[12]	16	F	10 months	—	×	Sudden mild sub-scapular pain	20 days	1,000–1,500	Yes	Yes	Yes	Yes, causing death	×	×	Autopsy showed a communication between pleural bleb and abdomen.
7.	Street[13]	24	M	5 months	+10	Attack of vomiting	Sudden dyspnea	Several hours	800	×	—	—	—	×	×	Pt. received right therapeutic PNX and PNP concurrently. After rupture, increased air seen in pleural space.
8.	Wynn-Williams[14]	44	M	6 months	+12 +15	Coughing	Pain in right shoulder and chest. Marked dyspnea	Several hours	1,000	Yes	—	×	×	Right phrenic	4½ months	Thoracoscopy revealed a bright red area on the diaphragm.

Abbrev.:

1.) PNP = Pneumoperitoneum
2.) PNX = Pneumothorax
3.) × = Negative finding
4.) — = Not given

TABLE 1—*Continued*

Case No.	Author	Age	Sex	Duration of PNP	Average PNP Press.	Precipitating Factors	Symptoms at Onset	Time after Refill	Aver. Amt. of Refill	Bleb Formation on X-Ray	Pleural Aspiration Performed	PNP Cont. after PNX	Recurrence of PNX	Phrenic Interruption	Time of PNX after Phrenic	Remarks
9.	Ross and Farber[4] Case I	24	F	14 months	+10 +12	Defecation	Dyspnea, substernal burning, palpitation	—	600–700	×	×	Yes	Yes	×	—	PNP induced twice and PNX occurred both times.
10.	Case II	58	M	15 months	+10 +12	Lifting and carrying	Severe dyspnea	—	800–1,000	×	×	Yes	×	Left phrenic	15 months	
11.	Case III	20	F	16 months	+7	×	Right chest pain, extreme dyspnea, weakness, palpitation	5 days	1,000	×	Yes	Yes (after pleurodesis)	×	×	×	PNX was continued. After 11 months PNP was resumed without incident.
12.	Repa and Jacobson[19]	22	M	15 months	+10 +12	×	Chest pain, dyspnea, shock	13 days	800–850	Yes	Yes	—	—	Right phrenic	13 months	Thoracoscopy showed a 1 cm. slit in the diaphragm.
13.	Wu and Neptune[26]	40	F	3 days	+8 +10	×	Dyspnea	Several hours after 1st refill	1,000	×	Yes	×	×	×	—	—
14.	Epstein[27]	21	M	12 months	+18	×	Sudden right chest pain, dyspnea	4 days	1,200	×	Yes	Yes	Yes	Left phrenic	11 months	PNX occurred 4½ months after resection of left lower lobe and partial thoracoplasty.
15.	Jones and Yuill[20]	28	M	4 months	+10	Lifting	Right chest pain, increasing dyspnea	1 day	1,000	×	Yes	Yes (for 2 refills)	×	×	×	At thoracoscopy, two black areas in pleural covering of tendon of diaphragm were noted.
16.	Miller[16] Case I	32	F	20 days	+7	×	Fever, neck tenderness, tachycardia	5 days	1,000	×	×	×	×	×	×	4,000 c.c. of air given within 15 days of induction. Thoracoscopy showed varicosities, fibrin deposits and adhesions.
17.	Case II	31	M	4 months	+7	Bending	Tightness in chest, severe dyspnea, cyanosis	24 hours	700	Yes	Yes	×	×	Left phrenic	4 months	Fluoroscopy following PNX revealed a bleb above the diaphragm.

TABLE 1—*Continued*

Case No.	Author	Age	Sex	Duration of PNP	Average PNP Press.	Precipitating Factors	Symptoms at Onset	Time after Refill	Aver. Amt. of Refill	Bleb Formation on X-Ray	Pleural Aspiration Performed	PNP Cont. after PNX	Recurrence of PNX	Phrenic Interruption	Time of PNX after Phrenic	Remarks
18.	Nozzoli et al.[28]	22	M	13 months	+20 +26	×	Right chest pain, intense dyspnea, cyanosis	8 days	—	—	Yes	Yes	Yes	×	×	Continuation of PNP caused peritoneal effusion and 6,000 c.c. fluid were removed.
19.	Riegel[21] Case I	35	F	12 hours	3500 c.c. air introduced at laparoscopy					Left PNX developed. 300 c.c. of pleural air were removed.						
20.	Case II	66	M	PNP induced for laparoscopy						Subcutaneous emphysema developed, followed by right PNX.						
21.	Lawton[5]	34	F	23 months	+10 +12	—	Right scapula pain, marked dyspnea	4 days	—	Yes	Yes	×	×	Left phrenic	23 months	Hydro PNX developed; 4400 c.c. fluid removed from right chest.
22.	Vysniauskas[29]	34	F	1 day	—	—	Tightness in chest, right shoulder pain, dyspnea	Immediately after induction	—	—	—	Yes 1 refill	—	—	—	—
23.	Vaid[20]	20	F	6 months	+12 +14	Straining at stool	Right chest pain, dyspnea	4 days	900	Yes	Yes	Yes	Yes	×	×	Right PNX was maintained and PNP abandoned.
24.	Breathnach[6]	18	M	7½ months	+8 +12	Hopping out of bed	Extreme dyspnea, cyanosis, irregular pulse	5 days	1,000	×	Yes	×	×	×	×	—
25.	Koelsch[31]	30	F	Several months	+3	Severe cough	Severe dyspnea	7 days	1,000	×	Yes	×	×	Right phrenic	Several months	—
26.	Montes Bazan[32]	21	M	3½ months	+12 +14	×	Right chest pain, dyspnea	15 days	1,000	×	×	×	×	×	×	Treatment was continued with right PNX.
27.	Belbenoit[12]	27	F	Same day	—	—	—	Immed. after induction	600	Yes	×	Yes	Yes	×	×	2 blebs seen immediately after induction. Left PNX seen that day. Treatment continued with left PNX.

TABLE 1—*Continued*

Case No.	Author	Age	Sex	Duration of PNP	Average PNP Press.	Precipitating Factors	Symptoms at Onset	Time after Refill	Aver. Amt. of Refill	Bleb Formation on X-Ray	Pleural Aspiration Performed	PNP Cont. after PNX	Recurrence of PNX	Phrenic Interruption	Time of PNX after Phrenic	Remarks
28.	Johnson[33]	59	F	5 months	+9 +11	—	Dyspnea and orthopnea	About 7 days	1,000	×	Yes	Yes	Yes	×	×	Sudden turning movement again caused PNX 2 months later.
29.	Sichinava[34]	39	M	4½ months	—	—	Severe dyspnea and cyanosis	6 days	500–1,000	×	×	Yes	Yes	×	×	—
30.	Guilleaudeu[7] Case I	24	M	7 months	+14 +20	×	Right chest pain, dyspnea	6 days	1,050	Yes	Yes, after 2nd PNX	Yes	Yes	×	×	An air-filled bulla of right diaphragm slowly developed on roentgenogram and ruptured twice.
31.	Case II	19	M	6 months	+8 +10	×	Ache in right chest, dyspnea	3 days	750	Yes	Yes	×	×	×	×	—
32.	Case III	31	M	9 months	—	×	Abdominal pain radiating to right chest	24 hours	750	Yes	Yes	×	×	×	×	
33.	Howells[23] Case I	25	F	30 months	+12 +15	Cough	Right chest pain, dyspnea	4 hours	1,000	×	×	×	×	×	×	—
34.	Case II	34	M	7 months	+2 +7	Cough	Ache in chest, dyspnea	Several hours	1,000	×	Yes	×	×	Left phrenic	7 months	Thinned right diaphragm noted before left PNX occurred.
35.	Case III	35	M	9 months	+8 +15	×	Left chest pain, dyspnea, pulmonary edema	During refill	—	×	Yes	×	×	Right phrenic	9 months	Left PNX seen on x-ray. Patient died same evening.
36.	Present case	34	M	26 months	+12 +16	Straining at stool	Abdominal pain radiating to right chest	2 days	800	×	×	×	×	×	×	Thinned-out right diaphragm noted shortly after induction of PNP.

both respiration and increases in intra-abdominal pressure in a case of spontaneous pneumothorax complicating pneumoperitoneum therapy. A similar bleb at surgery consisted of a hernia of peritoneum through a defect in the right dome of the diaphragm, the hernia being enclosed by parietal pleura (figure 5). These blebs have usually been described prior to the occurrence of rupture, although in one case it was seen on fluoroscopy after the pneumothorax had taken place.

This complication may occur at any age, but most of the cases reported have been in the younger age group. Of the 36 cases, four were below the age of 20, 25 were between 20 and 40, and five were over 40. The sex incidence appears to be about equal.

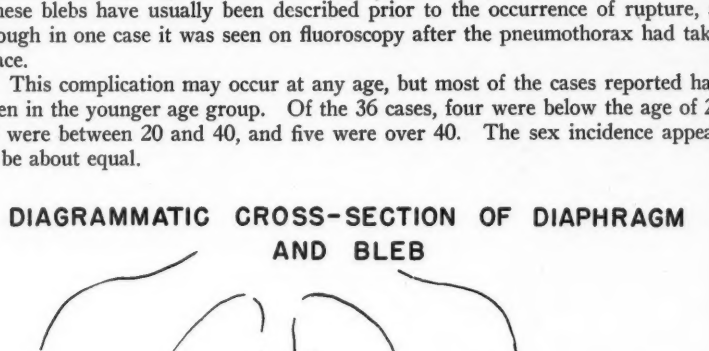

FIG. 5. Diagrammatic cross-section of diaphragm and bleb. (Courtesy Oritt and Hyde.[17])

The almost constant occurrence on the right side has been mentioned previously. Thirty-one of the 36 cases showed right-sided pneumothorax, four were on the left, and one was bilateral. Of the four left-sided cases, two occurred immediately after induction and one showed abnormal thinning of the right dome of the diaphragm, with subsequent left pneumothorax.

The intra-abdominal pressures reported have not been excessive, nor have the average amounts of refill been greater than those usually given in pneumoperitoneum therapy. It has been suggested that atrophy of the diaphragm following phrenic interruption might be a predisposing factor, but a review of table 1 shows that phrenic paralysis is of no significance. Of the 36 cases tabulated, 11 had phrenic interruption, and of these, five were of the left phrenic. One of the left-sided cases had had a previous right phrenic crush.

Many of the cases have occurred some time after pneumoperitoneum refill. This delayed rupture of the diaphragm may be due to the fact that intrapleural as well as intraperitoneal pressure is elevated immediately after refills. Several days later the intrapleural pressure tends to decrease practically to normal, and it is at this time that the difference in pressure between the two cavities is greatest.[25]

Up to the present time, only three fatal cases have been reported, although Howells felt his case may have died as a result of mediastinal emphysema. Smith's case died a few hours after pneumoperitoneum was induced. In the case described by Yannitelli, pneumoperitoneum was continued and death occurred five months after the pneumothorax. It is surprising that more deaths have not resulted, since a review of table 1 shows that, of 15 cases where pneumoperitoneum was continued, 10 had a recurrent pneumothorax. There is no doubt that more cases would have ended fatally had not prompt treatment been readily available.

The onset of symptoms may occur gradually if the diaphragmatic opening is small. However, an abrupt onset with severe dyspnea speaks for a much larger opening or sudden rupture. As the symptoms persist and show signs of increasing, the diagnosis of tension pneumothorax can be made. This requires immediate aspiration of air from the pleural cavity. Of the 36 cases, 21 required such aspiration, with resultant decrease in the severity of symptoms. Just why the tension pneumothorax develops in some cases is not clear. Some have felt that the abnormal opening in the diaphragm may act as a valve allowing air to be sucked into the chest in inspiration but preventing its escape back into the peritoneal cavity during expiration. Also tending to favor such a valvelike action is the alternate expansion and contraction of the dome-shaped diaphragm during the movements of respiration.

In the present case no bleb formation was noted, but from the time of induction the roentgenogram showed marked thinning of the medial half of the right dome of the diaphragm. Since this was present before any long-continued pressure from below could have produced stretching and weakening, it is felt that a congenital weakness of the diaphragm existed at this point and the further increase of intra-abdominal pressure above that of the pneumoperitoneum resulted in rupture and air leakage into the right pleural cavity.

Summary and Conclusions

1. A case of spontaneous pneumothorax complicating pneumoperitoneum therapy has been presented.

2. A review of the literature shows that most cases have occurred on the right side, usually some time after the induction, that they are usually sudden in onset, with chest pain and dyspnea, and are always associated with a simultaneous decrease or absence of the pneumoperitoneal air.

3. The cause is usually a result of rupture of herniated peritoneum through a weakened diaphragm, although rare cases due to congenital defect in the diaphragm may occur at the time of induction.

4. A significant number of cases have shown diaphragmatic bleb formation prior to spontaneous pneumothorax. These blebs are the visible evidence of herniated peritoneum.

5. The appearance of blebs or pneumothorax during the course of pneumoperitoneum therapy should be a warning against further continuance of this mode of therapy.

Addendum

Marolla et al.[35] have recently described an asymptomatic right-sided spontaneous pneumothorax in a 29 year old female, occurring two days after induction of pneumoperitoneum. Six months later segmental resections of the right upper lobe were performed, at which time examination of the diaphragm revealed a defect in the outer crus, with absence of muscular attachments to the lateral chest wall. The space, usually occupied by muscle, was filled with connective tissue. There was no evidence of herniation into the thorax.

Summario in Interlingua

Inter le plus que 40 complicationes observate in casos de therapia a pneumoperitoneo artificial, spontanee pneumothorace es listate como un occurrentia de relativemente basse frequentia. Es describite 37 tal casos in le litteratura medical del mundo. Le majoritate de istos occurreva al latere dextere, probabilemente a causa del facto que le pneumoperitoneo elimina le supporto del diaphragma que es normalmente representate per le hepate. Tractos characteristic de iste complication es un subitanee declaration de dolores thoracic e dyspnea associate con un simultanee reduction o disparition del aere intraperitoneal. In casos rar le complication occurre al tempore del induction del pneumoperitoneo, usualmente in consequentia de congenite defectos del diaphragma. Le plus frequentemente le pneumothorace es causate per un ruptura del diaphragma. In iste ultime gruppo de casos on pote supponer le presentia de un congenite debilitate diaphragmatic. Le constante e prolongate pression pneumoperitoneal resulta postea in un debilitation e tension additional usque un phlyctena de peritoneo forma un herniation a in le cavitate pleural. Un leve augmento additional del pression intra-abdominal suffice alora pro causar le ruptura del phlyctena. Plure autores ha describite tal bullas a contento de aere occurrente in le area del domo diaphragmatic ante le occurrentia de spontanee pneumothorace.

Le majoritate del casos de spontanee pneumothorace ha occurrite alicun tempore post le replenamento pneumoperitoneal, quando le differentia inter le pressiones del cavitates pleural e peritoneal attinge un maximo. Le causation del passage de aere non depende significativemente de altere factores, como per exemplo le pressiones pneumoperitoneal, le quantitate de aere usate in le replenamento peritoneal, e previe interruptiones phrenic.

Le complication hic discutite pote haber serie consequentias. Il existe reportos de tres casos mortal, e in 21 del 37 casos le uso de aspiration pleural de aere esseva necessari pro alleviar le tension.

Es presentate un caso, e le disponibile datos clinic de omne casos trovate in le litteratura es tabulate.

Le autor conclude que le apparition de un phlyctena diaphragmatic o le occurrentia de spontanee pneumothorace in le curso de therapia a pneumoperitoneo artificial deberea esser interpretate como signo que le continuation de iste modo de therapia non es indicate.

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MYXEDEMA IN TWO BROTHERS, ONE WITH PSYCHOSIS*†

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INTRODUCTION

MYXEDEMA is uncommon in young males and its occurrence in siblings is rare. It is a common but frequently unrecognized cause of organic psychosis.

Nearly half the patients cited by the Committee on Myxoedema [1] had some form of mental disturbance. The psychotic manifestations of myxedema may exhibit themselves before the classic picture of the disease has developed and may be the first obvious evidence of altered thyroid function.[2] The psychosis which is dependent on myxedema occurs in 15% of patients, usually when the myxedema is advanced.[3] This psychosis does not represent any specific type, but there is common behavior characterized by confusion, disorientation, persecutory delusions, hallucinations, and bouts of restlessness and violence.[4]

Myxedema may precipitate a psychosis in an individual with latent psychotic tendencies. In such a patient the type of psychosis may be determined by the premorbid personality.[3] Psychosis with myxedema is due more to the specific psychologic characteristics of the individual than to the organic changes in the thyroid gland. A deep-lying mental disorder exists, brought into prominence by a disturbance in the functioning of the brain associated with the disturbed metabolism.[5] This condition is amenable to treatment with desiccated thyroid. If it is recognized, institutional care may be avoided.

Asher reports 14 cases of "myxoedematous madness" in four years of practice.[4] None of these had been correctly diagnosed before admission to the hospital; 10 had been declared insane and committed to mental institutions.

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Case Reports

Two brothers developed myxedema within six months of each other, one with psychosis.

Case 1. W. B., a 19 year old male, was seen at his mother's request in January, 1951, because of unusual behavior. This had been first noticed six months earlier, at the time of his graduation from high school, and was manifested by increasing confusion, irritability, paranoid ideas and seclusiveness.

The patient was the second son of an Italian-born father and an American mother. The siblings included two sisters, 18 and 14 years, and three brothers, 20, 17 and 12 years of age. The father, a 45 year old restaurant owner of peasant stock, had had little education. He had always been an excessively hard worker, and demanded a similar performance from his family. He was a rigid disciplinarian and often inflicted brutal physical punishment on his wife and children. His behavior was at times unpredictable and was characterized by violent outbursts of rage, so much so that he had intimidated his family. The mother, 45 years old, of New England stock, spent her life attempting to meet the demands of her husband, and to raise her children and protect them and herself from the attacks of her husband. Shortly after the birth of the patient the father manifested intense resentment of his second-born son and of the time his wife spent with the child. His behavior was such that the mother was often forced to take the child to her parental home, where he was cared for by his grandmother.

Both parents, particularly the father, put great emphasis on success, and had plans for the four boys to have college educations. The parents worked relentlessly, often doing the most menial jobs late at night, to save money for the education of their children.

The father was intensely resentful of W. B. for his lack of interest in a college education, and often berated him for hours at a time for his laziness, lack of interest and lack of desire to improve himself.

The patient's birth and early development had been normal. With the exception of a middle ear infection at five years of age and the usual childhood diseases, his health had been good. There had been no operations or accidents. His parents and siblings were in good health. A maternal aunt had had myxedema, with a good response to desiccated thyroid. There were no other endocrine or familial diseases in the immediate family. A review of his health record at the local school showed the expected yearly increase in weight until 1950–1951 (the year of his graduation and illness), when there was a gain of 15 pounds. There were no unusual dietary habits, and there was no history of exposure to goitrogens.

During his prolonged illness from middle ear infection at the age of five, his father became particularly irascible and had violent outbursts of temper directed toward both the mother and the child. The mother turned her attention increasingly to the child in an attempt to protect him. The boy remained in poor health and missed the first year of school. He was withdrawn and overly attached to his mother, and seldom participated in the games of his siblings and friends. His performance at school was such that he was barely passed from year to year. He rarely took part in organized sports. His younger brother, R. B., only a year behind him, had always done well in school work, was an excellent athlete and had a wide circle of friends, a source of considerable discomfort to the patient. The teachers in general seldom took much interest in W. B., and one openly ridiculed him both in and out of class. In his senior year this teacher relieved the patient of his position as baseball manager without explanation several months before his graduation and gave the job to R. B.

Whenever he was ridiculed or reprimanded he maintained an angry silence, never answering back. His sister characterized his behavior on such occasions as

that of "clenched fists." His withdrawn behavior and sullen attitude were increasingly noticeable during the last six months of his schooling. His one outside interest was playing the saxophone in the dance band. This band was directed by a farmer, the father of a large family who made extra money in this way and who had taken considerable interest in the patient. Several months before the boy's graduation the farmer had remarked on his increasingly peculiar behavior, his growing irritability, seclusiveness and unpredictability. The boy would occasionally fail to keep engagements and would appear bewildered when asked why he had failed to appear.

The parents had also remarked upon the boy's behavior and had discussed it with the friend, but they felt it was simply an accentuation of his normal behavior and probably due to the stress and strain of graduation.

Several weeks after graduation the boy's maternal grandmother died suddenly. She had acted as a bulwark for both mother and son against the father when his behavior became unbearable. Her home, which had been a refuge for them, was no longer available. The boy was inconsolable.

When the boy's abnormal behavior continued after graduation and became more noticeable the mother became alarmed. The father, on the other hand, increased his demands upon the boy, insisting that he get out and get a job. When the boy replied by spending longer hours locked in his room and working on his radio the father became enraged and punished him.

In August the boy volunteered for the Army but was rejected. The grounds were not specified. His parents knew nothing of this until he confided in his mother that he was useless, that not even the Army would take him. He became increasingly depressed, did not leave his room at all, and would take food only when it was carried to him by his youngest brother.

During the fall and winter he had abscessed teeth. The mother, grateful for a chance to separate the boy from his father, took him to Boston on the pretext of having his teeth fixed, but more because she wished to have a medical opinion concerning the boy's behavior. The father had previously refused to allow the boy to visit a physician, saying that he was simply lazy and good-for-nothing, and that he was going to throw him out of the house.

In late December he was first seen by W. N. C. at the mother's request. He appeared depressed and confused, though he was effusive in expressing appreciation for the interest shown in him. He had definite paranoid ideas. It was noted that his skin was pale and his face puffy. The mother stated that his appearance had not changed for several years. Physical examination revealed nothing else of significance. He was referred to a psychiatrist, who made a diagnosis of mild confusional state with schizoid coloring. The possibility of early schizophrenia was considered. Under psychiatric treatment he seemed to show gradual improvement over a period of three weeks. He became clear mentally, was optimistic and seemed to have considerable insight into his problems. However, six weeks after the original visit he again became depressed, cried frequently, and expressed fears of criticism by others for his failure to "do something on my own."

Because of the exacerbation of symptoms and increasing puffiness of his face he was referred for medical review. At this time he appeared more withdrawn, suspicious and depressed than previously. His actions and speech were slow, indecisive and often inappropriate. His voice was hoarse and croaking; his facial puffiness was definitely increased. The blood pressure was 140/100 mm. of Hg. in both arms. The pulse was 70, the temperature 98° F. The skin was smooth. The hair and finger-nails were not dry or brittle. The thyroid gland was palpable, but not enlarged or of unusual consistency. The reflexes were considered normal. Other physical findings were entirely normal.

It was felt that there had been a striking change in the boy's physical condition in six weeks. A tentative diagnosis of myxedema was made. Psychotherapy was continued during investigation of the thyroid status. The basal metabolic rate at this time was minus 6 and minus 9. The serum cholesterol was 305 mg.%. The hemoglobin was 11.6 gm. by the Klett photometer method. The cardiothoracic ratio by x-ray was 15.5 to 28.2, suggesting slight cardiac enlargement. The electrocardiogram showed nonspecific T wave changes. Admission to the hospital was advised for further study and treatment. At first the patient was resistant to this idea, saying, "It is all up to me. I've got to get courage and build up my strength. . . ." However, he finally consented and was admitted to the Mary Hitchcock Memorial Hospital, two months after the original examination and 10 months after his abnormal behavior was first noticed. His mental confusion had increased and he would respond to questions only after several queries. There were increased puffiness of the face and dryness of the skin. The deep tendon reflexes were now consistent with myxedema. The physical examination was otherwise unchanged. The basal metabolic rate at this time (one month after the initial basal) was minus 25 and minus 26. The serum cholesterol was 344 mg.%. The hemoglobin was 11.9 gm., the white blood count was 9,000. There were 76 segmented polys, 1 stab, 22 lymphocytes and 1 eosinophil. The erythrocyte sedimentation rate was 18 mm./hr.

The urine specific gravity was 1.025. There was no albumin, sugar or bile. There were 10 white blood cells and 20 red blood cells per 10 high power field. The fasting eosinophil count was 106/mm.^{3} Fifteen milligrams of ACTH were then given intramuscularly and the count was repeated in four hours, at which time there were 13 eosinophils/cu. mm.; repeated two days later, fasting, 38 eosinophils/cu. mm.; four hours later, 44 eosinophils/cu. mm. The blood sugar was 73 mg.%. Cardiac fluoroscopy confirmed the original impression of slightly enlarged heart and slow rate. The skull x-rays were negative. The electrocardiogram showed sinus bradycardia and nonspecific T wave changes consistent with myxedema heart.

Early in the hospital course he exhibited frankly paranoid behavior and had auditory hallucinations. He became increasingly agitated and confused. As there were no facilities for handling psychotic patients over a prolonged period of time, transfer to a psychiatric institution was seriously considered. However, in view of the probable cause for the psychosis and the good prognosis in such cases, it was decided to start thyroid treatment and to defer institutionalization. Accordingly, an initial daily dose of 7.5 mg. desiccated thyroid U.S.P. was given. This was continued for one week without untoward effects, and was gradually increased each week until, at the time of his discharge four weeks later, he was taking 120 mg. daily.

During this time the paranoid behavior and hallucinations continued. He spent considerable time listening to imagined voices which he said were talking about him: "I'm a coward. The others are out there dying . . . and look at me." At other times he would speak of "strange surging sensations" within himself, "as though something was about to break; something I can't control."

There was considerable display of intense guilt concerning sexual feelings. One night he slept poorly: "I had a strong sexual urge and had to fight it all night." He became suspicious of his medication and asked what it would do to "the glands down there." He misread the label on his breakfast tray which said "Annex 5." He thought it read "Homosexual 5."

A note was found at his bedside: "God and Dr. C. gave me plenty of chances to make good." He began having periods of excessive activity about a week after thyroid was begun. He did setting-up exercises for an hour at a time; any attempt to stop him would result in considerable anxiety and more agitated behavior. These periods alternated with periods of being withdrawn, communing with himself, moving his lips but not speaking. Long silences would occur when he was visited by the

physician, nurses or his friends. Often only a few words would be spoken in a half-hour visit. Throughout his hospital course strong supportive psychotherapy was given. The resident intern, nurses and attendants all took part in this supportive program. The physician in charge visited him at least twice a day, spending a minimum of half an hour and often more time with him. These sessions were often spent in silence save for occasional, slowly spoken words. These silences were not strained. A college student who was particularly interested in him sat with him throughout the nights during the particularly disturbed period.

Two weeks after beginning thyroid he began to show increased facial expression, and there was less puffiness. There was more ease of bodily movements, and he talked more freely. He had lost four pounds. He continued to be puzzled, and was extremely subservient and unable to make simple decisions for himself.

When topics such as the weather were talked about the patient would listen with interest, though not participating. When things were discussed which were emotionally laden for him he would become anxious and withdrawn. However, an attempt was made to talk of guilt feelings and hostility in a general way. Gradually he showed less anxiety in these conversations. He began to listen with interest, though he would react intensely to whatever was said by facial expression and motions of the body.

When he had been on thyroid for approximately a month he began to relate himself more to reality and seemed to be developing some insight. He began talking, though with much hesitancy, often beginning a sentence and not finishing it. He said: "A lot has happened in the past month. Do you think it is for the best?" His skin was now warm and moist. The basal metabolic rate had risen to minus 14 and minus 19, and the serum cholesterol had dropped to 141 mg.%.

The sudden bursts of motor activity became more striking. Occasional rage reactions would occur while he was with his parents. On one occasion, while out for a drive with them, he suddenly demanded to be allowed to drive. He proceeded to drive at a high speed on a narrow winding road. His parents were terrified and managed to stop him only after repeated commands. One evening while playing ball with his attendant he suddenly ran off and agilely scaled the four-story scaffolding on the new hospital. He would suddenly dart out of his room and down the halls, obviously enjoying the excitement and chase that ensued.

It was felt that these manifestations were healthy reactions, indicating his feeling that he could throw over the traces. However, it did indicate poor judgment, which might endanger others as well as himself. Institutionalization was again considered. However, when definite limits were indicated, and he was put to work with the engineering crew of the hospital, he became more reasonable in his activity. At the same time his attendants were dismissed, as it was recognized that he resented their presence and they increased his paranoid tendencies.

It was pointed out to him that he could have as much freedom as was reasonable so long as he demonstrated that he could accept the responsibility and not break the trust in him; otherwise, the privileges would be withdrawn. He seemed pleased with this.

His improvement continued. He was delighted with his freedom and was eager to show his appreciation. He smiled more appropriately and his speech became freer. Long lapses between sentences still occurred, and occasional catatonic attitudes persisted in which he would remain for hours at a time with his arms raised above his head. After a long period of silence he said: "I'm not as strong as others. I have no muscles. I'm different from others. At my age I should be on my own, self reliant and with a trade."

He had previously shown considerable interest in radio. A partially completed set was obtained for him and a student interested in radio spent each afternoon help-

ing him with it. He showed great interest in this and said that he wanted to continue his correspondence course in radio. He continued to do well, and was punctual about the hours of his work with the engineering crew. His performance was excellent while on the job or out walking with friends. However, when he was not able to go out to work, or if he was frustrated in some way, he would become unruly, dash about, threaten the nurses, hide in closets, all in a childish way and grinning sheepishly when reproved.

About two months after admission he said: "When can I go home? Mr. M. was right. He always said I was unstable and he thought the best thing for me was to go into the service. Society is here. I'm over here." It was pointed out to him that he had improved so much that the distance between society and himself had decreased a great deal. He continued to improve, talking more freely of his own feelings and showing more spontaneity, humor and appropriate mood reaction.

In view of his improvement discharge from the hospital was considered advisable, but it was thought best not to send him home because of his intense emotional reaction to both parents and the unpredictability of his father's behavior. He had often spoken of his admiration for the farmer in whose band he had formerly played the saxophone. This man and his wife were interviewed. They were solid citizens—warm, understanding, acquainted with the problems of children through their own four offspring. They were eager to take him on their farm in return for his work, the wages for which would be paid by his parents, though this was unknown to him. He was delighted with this plan. Accordingly, arrangements were completed and the physician in charge took him to his home to get clothes prior to going to the farm. While upstairs with his mother for a few minutes he suddenly turned on her and hit her on the jaw. Hitherto his parents had resented the fact that he was not being allowed to return to his own home, but following this event they were more agreeable to the arrangements.

He was obviously very upset by his encounter with his mother, but was happy when he arrived at the friend's farm, where he was warmly received.

He immediately adjusted himself well to his new life and became a valuable assistant on the farm. He used considerable ingenuity and worked hard. During these weeks he was seen at weekly intervals by the physician. He expressed a desire to start a chicken farm on his own. He also asked to see his mother, who came immediately. There was obvious demonstration of affection on both sides. He did not wish to remain with his friends but was eager to go to his parents' farm and start raising chickens.

Two weeks later he went up to his parents' farm, where he remained alone at his request, his family writing to him each day. On one occasion his father had an outbreak of rage at him, but he took the incident without any undue demonstration of anxiety. His improvement continued. He was now talking freely, laughing readily, and working very hard on the farm. He began studying radio again and continued his plans for a chicken farm. For the first time in their lives the father and son found enjoyment in each other: "We have a wonderful time together." The father was glowing with pride in his son's accomplishments. His interests became entirely centered in radio and he began working excessively at this, often staying up until three or four in the morning. He gave up the idea of a chicken farm. He was now making plans to get a job in a large Boston radio corporation for the winter and to live with his cousin, who had shown considerable interest in him and had helped him with his radio work. His parents continued to be threatened by his recurrently belligerent attitude toward them. However, they were reassured when it was pointed out to them that this was to be expected and was a healthy sign.

He was now receiving 120 mg. desiccated thyroid (U.S.P.) daily. Physically

he appeared completely normal. His final basal metabolic rate was minus 7 and minus 9. The serum cholesterol remained at normal levels. His hemoglobin determination had risen to 13.4 gm. The electrocardiograms were now considered to be within normal limits save for sinus bradycardia. He had lost a total of 13 pounds in two months.

Because it was considered important to understand the nature of the thyroid disturbance, and because the patient had made such a complete recovery, a biopsy of the thyroid gland under local anesthesia was attempted six months after institution of thyroid. Although he showed no unusual anxiety before the procedure, he had a syncopal episode when the incision was being made. Accordingly, no biopsy was taken. When this was explained to him he asked if he might have it done the following day. This was decided against and the procedure was deferred indefinitely.*

When he was seen two weeks later he again offered to have the biopsy done. He had procured the radio job in Boston which he had been planning on and had decided to study radio in his spare time. He was to live at his cousin's home. Repeat basal metabolic rates and serum cholesterol were normal.

He was seen at Thanksgiving time, a year after his original visit and 10 months after the beginning of thyroid administration. He was looking very well and reported that he was happy with his job and his new life in Boston. He talked freely and with considerable pride in his work. He stated that he was enjoying association with his fellow workers, a new experience for him.

Two months later he returned for a check-up and said that he had volunteered along with other men from the radio corporation for duty in the Armed Services. He had not told of his illness. He was strongly urged to report his illness to the authorities, and was given a letter describing his myxedema with psychosis. Two weeks later word was received that he had been accepted by the Service.

At this writing it is two years since his induction and three years since onset of the myxedema. He has performed excellently, is well, and reports that he is happier now than he has ever been in his life. He continues to take desiccated thyroid (U.S.P.), 180 mg. daily.

The Service has shown its confidence in him by sending him to the advanced school for training in radio, where he has received a superior rating. He has the rank of S/Sgt. He is now attending college with support from the Army.

Case 2. Six months after W. B.'s first visit R. B., his 17 year old brother, sought medical attention because of continued bleeding from the gums. This had continued for four days after the extraction of an abscessed tooth. Excessive bleeding occurred at the time of extraction, and four sutures were required to arrest it. Despite this, oozing persisted. He had never noted unusual bleeding before. There was no familial bleeding tendency.

He stated that he had always been in excellent health. A grade II basal systolic murmur had been found on routine physical examination three years previously. After thorough investigation the murmur was considered of functional origin.

When he was questioned more closely (with his brother's problem in mind), it became apparent that for the preceding six to seven months he had been unusually fatigued. He felt like sleeping more than usual and thought that the cold bothered him more. He had lost 15 pounds in the preceding six months but had been doing unaccustomed hard physical labor. He could sleep at any time during the day but would awaken refreshed. His work performance was excellent. He was able to work as hard and as long as his companions. His appetite was good and his bowels were regular. He had just been graduated from high school with excellent marks.

* It is assumed that W. B.'s diagnosis is chronic thyroiditis on the basis of the proved diagnosis in the case of R. B.

No history of exposure to goitrogens could be obtained. There had been no neck or throat pain.

Physical examination revealed a well developed but pale and slow-speaking young male with a hoarse voice. The blood pressure was 110/70 mm. of Hg; pulse, 48; weight, 125½ pounds. The skin was dry and coarse and the hair fine. There were no abnormalities of the head, eyes, ears, nose or throat. The thyroid gland was palpable but not enlarged. The lungs were clear. The heart was not enlarged. There was a grade II basal systolic murmur as described before. There was no diastolic murmur. The liver edge was palpable one fingerbreadth below the right costal margin. There were normal hair distribution and normal secondary sexual characteristics. The reflexes were brisk but there was a delayed relaxation phase.

The specific gravity of the urine was 1.022. There was no sugar or albumin. There were 3 white blood cells and 15 red blood cells per 10 high power field. The hemoglobin was 11.2 gm., and there were 3,550,000 red blood cells. The bleeding time was 5½ min. and the clotting time 5½ min. Fluoroscopy of the heart showed no abnormality, and the lung fields were clear. The basal metabolic rate was minus 39 and minus 40. The serum cholesterol was 178 mg.%. The electrocardiogram showed sinus bradycardia and low T waves throughout, consistent with myxedema.

Biopsy of the thyroid gland was performed under local anesthesia with no untoward effects. The gland was firm, and unusually yellow; the gross size could not be accurately determined. The surface was smooth. The biopsy specimen consisted of a gray, firm, moderately granular, irregular tissue fragment measuring 1.5 cm. The microscopic examination revealed scattered thyroid follicles lined by cuboidal cells, with large nuclei and abundant eosinophilic cytoplasm. There was a large amount of lymphatic tissue throughout all sections, whereas fibrous tissue was present to a slight to moderate degree only. The pathologic diagnosis was chronic thyroiditis.

It was apparent that the classic histologic features of struma lymphomatosa were not present, and the diagnosis of chronic nonspecific thyroiditis was made.

He was started on 15 mg. desiccated thyroid (U.S.P.) daily. This was gradually increased to 180 mg. over a period of three months. He noted a decrease in fatigue and no longer felt drowsy during the day. His skin gradually became smoother. His basal metabolic rate was minus 33 two months after beginning thyroid. A year later the basal metabolic rate was minus 17 and minus 25; his blood pressure was 130/80 mm. of Hg; pulse, 62. He had gained 10 pounds. The hemoglobin had risen to 14.3. The electrocardiogram had returned to normal. The myxedema reflexes had disappeared.

That fall, four months after the diagnosis was made, R. B. entered the freshman class at the University of New Hampshire. Although he did well at first and enjoyed the social life, by Christmas time his marks had fallen and he was given a warning. He failed to improve his standing and by spring was dropped. He spent the next summer studying, was re-admitted to the freshman class and again failed. At this time he was called up by the Army, but he requested deferment on the basis of his myxedema. This was granted. For the past two years he has been well physically and has been employed as a clerk. He has given up all aspirations to further intellectual and technical education.

It is of interest that the oldest brother had decided to be an architect but failed his college entrance examinations. He has subsequently had a job as draftsman but has no other plans.

The oldest sister has successfully completed a secretarial school course and is a source of considerable pride to her family.

The other two children are still in school and doing satisfactory work.

A complete medical survey was made of the six other members of the family

because of the unusual occurrence of myxedema in two brothers, both developing within six months of each other. The studies included a medical history, physical examination, routine laboratory work up, chest x-ray, electrocardiogram, basal metabolic rate and serum cholesterol. However, no evidence of endocrine disturbance was found. The only other member of the family with endocrine disease was the maternal aunt previously mentioned, with treated myxedema.

Etiology and Discussion

The pathogenesis of chronic thyroiditis is unknown, although the literature does not lack for theories. Bohan in 1924 suspected that dental abscesses and pyorrhea could be incriminated, and indeed produced changes in the thyroids of rabbits by injecting green streptococci and staphylococci from these sources.[6] Pedigo and Abramson reported on a patient with struma lymphomatosa associated with severe caries and pyorrhea which was treated by dental extraction and sulfadiazine, without improvement.[7] Nonspecific thyroiditis in rats was produced by McCarrison in 1929 by a vitamin-deficient diet.[8] Hellwig, in reporting on four patients with lymphadenoid goiter, postulated that thyroid-stimulating hormone was responsible for the change, and cited evidence that its use in animals produced a similar picture.[9] Joll, after a complete review of the subject, could come to no conclusive opinion regarding the etiology, but felt that it was a manifestation of obscurantism to refer to the process as inflammatory in nature.[10] In Womack's review he pointed out the similarity between the pathologic findings of this process and those occasionally seen in chronic adrenal cortical insufficiency.[11] When Marshall, Meissner and Smith reviewed the material at the Lahey Clinic they pointed out that thyroiditis is rarely seen before the age of 35 years, and that it is rarely seen in men. In only four out of 147 instances of chronic thyroiditis, of both the Hashimoto and the nonspecific type, were the patients male.[12] Crile in 1952 pointed out that chronic thyroiditis might represent an exhaustion response of the thyroid, and that the changes are reversible by putting the thyroid at rest.[13]

Myxedema as the result of chronic thyroiditis is a well recognized sequel of this condition.

An excess of thyroid-stimulating hormone has been demonstrated in the blood and urine of some patients with myxedema.[14] This has been interpreted as indicative of a pituitary activity which has preceded the hypothyroidism and has been so excessive as to cause secondary atrophy.

Thyroid suppression may result from cortisone and compound F.[15] Stress induces effects like compound F in decreasing thyroid function.[16, 17] There is evidence to indicate that the hypothalamus may control thyroid function by way of the anterior pituitary.[18]

Nervous impulses reaching the hypothalamus can indirectly excite activity of the anterior lobe of the pituitary gland. As the thyroid gland is normally regulated by the thyrotropic hormone, there may exist a neuroglandular mechanism by which the mental state can influence the activity of the thyroid gland. Fluctuations in the protein-bound iodine levels have been demonstrated in association with exposure to stressful life situations.[19] This explanation has at least been advanced to explain the occurrence of exophthalmic goiter after mental shock or prolonged anxiety. This hypothesis might also be ad-

vanced to explain the onset of myxedema under certain circumstances. A case of myxedema has been reported in a soldier following shell-shock.[20]

At the time of onset of their myxedema the brothers were of approximately the same age. They had the same hereditary, social and economic background. Physically they were much alike. They had been graduated from the same high school within a year of each other. They both had had dental infections but it is obvious, at least in the case of R. B., that the myxedema preceded the infection as his symptoms preceded the dental problem by six months. In the case of W. B. if onset of the abnormal behavior is taken as a manifestation of myxedema, this preceded the dental infection by three to four months. It is probable that the abscessed teeth developed secondary to the myxedema and aggravated it.

A definite answer to why the myxedema developed in the two brothers within six months' time cannot be given. But the cause for the different response of two individuals to the same disease is suggested by their personalities and their relationship with their father. One was confident, carefree, outgoing and gregarious. He enjoyed competition and was making a good heterosexual adjustment. He had made plans for his future. He had never been the object of his father's hostility and rages. The father loved and praised this boy as much as he despised and deprecated his older son. He was a good student and had always been interested in organized sports. He was well liked by his companions and had numerous friends. In comparing himself with his brother he said: "He sticks mostly to himself. He doesn't have any idea of getting out and getting himself a job. . . . He doesn't even go out with girls—he lacks confidence. . . . I like to go out with my friends and with the girls. I enjoy competing in athletics and in work with the other boys. I never like to stay at home by myself."

Myxedema in the case of this young man was found only by coincidence and the careful searching for symptoms. There were few but definite physical findings on which to make the diagnosis.

The other son lacked confidence, was intensely introspective and quiet, and avoided competition. He liked to be by himself. Although older, he had made no heterosexual adjustment. He was desperately attempting to find his way, but beyond struggling with a radio correspondence course he was unable to liberate himself in a normal way from his parental influence. This was in spite of his father's constant commands that he get out and get himself a job.

His anxieties concerning his failures and inability to make way for himself increased with his imminent graduation. He was graduated only after the intercession of a particularly interested teacher, and he refused to participate in the graduation exercises. With the death of his grandmother there was a further threat to his security. There was added stress from the dental infection. The father increased his demands and brutal attacks. In this setting he receded further from reality and defended himself by retiring into a world of his own. There was a collapse of his normal psychologic defenses, a schizoid state developed, and the evidence of thyroid insufficiency progressed rapidly to an extreme manifestation of the disease, with all the classic clinical findings appearing within a few weeks.

The subsequent performance of these two young men is of interest, since

R. B., who was the better adjusted and the better student, and whose illness was handled without disruption of his life, has failed college twice and has failed to accomplish his other objectives, and is satisfied to float with the stream, at present working as a clerk. His brother W. B., who was poorly adjusted and a poor student, and had a severe psychotic reaction during his illness, has succeeded in emancipating himself from his family, is successful in a highly technical skill, is acquiring a college education, and for the first time in his life is able to strike out on his own.

Summary

1. The cases of two brothers with myxedema, one with psychosis, are presented in detail.

2. The pathogenesis of chronic thyroiditis and some neuro-endocrine relationships of the thyroid are discussed.

3. The differing manifestations of myxedema and the subsequent courses of the brothers are considered in the light of their life histories, emotional development and treatment.

Summario in Interlingua

Myxedema non es commun in juvene masculos; su occurrentia in fratres es rar. Illo es un causa commun, ben que frequentemente non recognoscite, de psychosis organic. Es presentate in detalio le casos de duo fratres de etates de 19 e 17 annos qui disveloppava myxedema intra 6 menses le un post le altere; un del casos esseva associate con psychosis.

Le examine bioptic del glandula thyroide del plus juvene del duo fratres demonstrava thyroiditis chronic. Ambe patientes respondeva ben al tractamento con desiccate thyroide e psychotherapia supportante. Durante que le primogenite esseva retirate, morose, e pauco bon in su studios, le altere esseva gregari e popular e se preparava a continuar su studios post le fin del schola secundari. A causa del psychosis, le maladia del fratre primogenite esseva plus prolongate, e su vita esseva plus profundemente disrumpite. Post recuperar ab le maladia, ille ha grandemente superpassate su fratre in omne phases del vita.

Es discutite le pathogenese de thyroiditis chronic e le rolo etiologic de iste condition in myxedema. Es presentate un mechanismo neuroglandular per que le stato mental pote influentiar le activitate del glandula thyroide. Le differente manifestationes de myxedema e le differente cursos subsequente del morbo in le duo fratres es considerate in relation con le historia de lor vita, lor disveloppamento emotional, e le therapia usate in le duo casos.

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LEIOMYOSARCOMA OF THE SMALL BOWEL IN A CHILD*

By David B. Monheit, M.D., and George A. Degenshein, M.D.,
Brooklyn, N. Y.

In the past 10 years an ever increasing number of small bowel tumors has been reported in the literature. This is undoubtedly due in part to improved diagnostic technics and to a willingness to intervene surgically in cases of gastrointestinal bleeding with negative roentgenograms.

Since the number of small bowel sarcomas remains modest and the literature has been reviewed adequately by others, it seems hardly warranted merely to add another single case history to an already cluttered literature. However, in the case to be reported there are several instructive features: the age of the patient, the disturbing red herring of a suggestive heterophil agglutination, the complete absence of any abdominal symptoms, the absence of gastrointestinal bleeding, and the reiteration of the importance of repeated rectal and bimanual examinations in the course of an illness of obscure origin.

Case Report

A well developed, well nourished seven and one-half year old girl was admitted to the hospital on November 8, 1950, after having been treated at home for three weeks for a fever of undetermined origin. General physical examination was negative except for mild neck and groin adenopathy. The patient ran a febrile course, with

* Received for publication August 16, 1954.

daily elevations to 103° F. Abdominal palpation was negative, and rectal on admission was said to be negative. Laboratory data revealed a hemoglobin of 62%; red blood cells, 3.4 million; white blood cells 9,400, with 63 polymorphonuclears, 34 lymphocytes, 2 eosinophils and 1 monocyte. Urine was negative. Sedimentation rate, 64 mm./1 hr. Typhoid, proteus OX19, paratyphoid and brucella agglutinations were all negative. The heterophil agglutination was positive in dilution of 1:112.

Infectious mononucleosis was suspected and a medical régime was instituted. However, the patient lost ground steadily, her anemia became more severe and she appeared more toxic, though she had no complaints whatever except for the fever.

On repetition of abdominal and rectal bimanual examination a mass was felt the size of a tangerine which was hard, mobile and easily ballotable. In effect, rectal

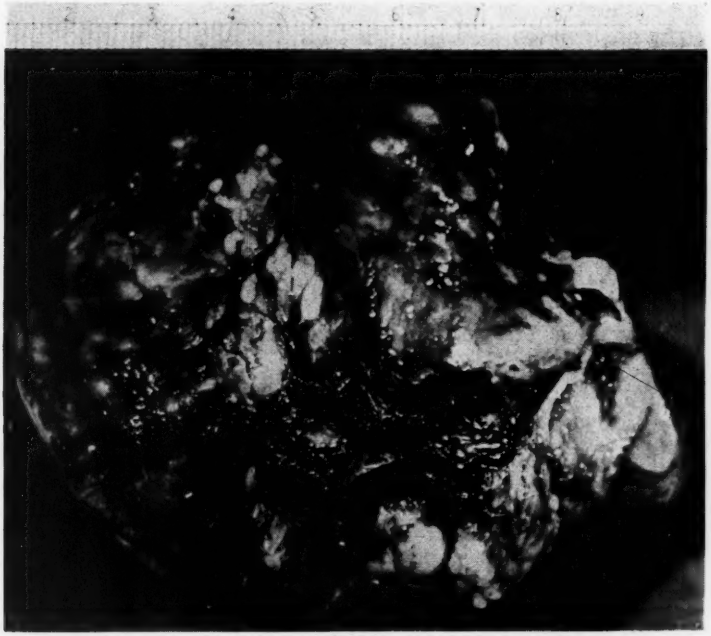

FIG. 1. Mass demonstrating the area of degeneration which undoubtedly accounted for the fever.

examination alone was negative, but when the abdominal contents were compressed from above the mass became palpable. A provisional diagnosis of degenerating tumor of the ovary was made and laparotomy performed after a transfusion. At operation a large solid mass was found attached by a short pedicle to the serosa of the distal jejunum. The mass contained a large area of degeneration on its under surface (figures 1 and 2). The mass arose from the outer coats of the jejunum, and there was no gross evidence of invasion to the mucosa. In view of this finding, and the marked debility of the patient, an elliptical incision was made about the pedicle and a local excision performed. The bowel was closed with two layers of chromic catgut No. 00. Though the question of malignancy was considered, it

was felt that local excision was all that was advisable in this weakened child, and that if the mass proved malignant a more extensive resection could be carried out at a later date.

The patient made an uneventful recovery, with a dramatic drop in temperature to normal on the first postoperative day, for the first time in seven weeks. She improved progressively. The pathologic report revealed the specimen to be a leiomyosarcoma (figure 3). The mucosa was intact but the other walls were involved. On the fifth postoperative day the patient was returned to the operating room, where a resection of 12 inches of jejunum on either side of the lesion was performed and an end-to-end anastomosis done. The pathologic specimen showed extension into the adjacent serosa; the mucosa was intact and the regional nodes were free from involvement.

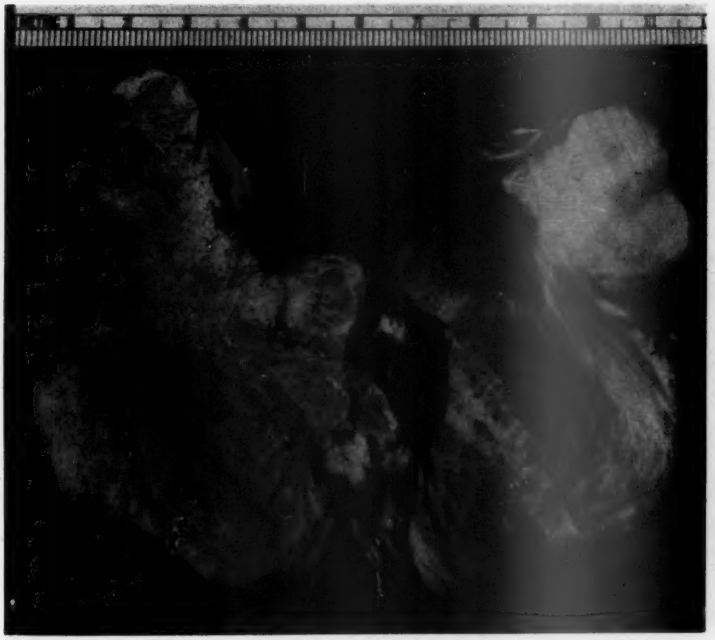

FIG. 2. Mass on cut section.

The patient was discharged on the seventh postoperative day after an uneventful recovery. At the present time, three and one-half years later, she has gained 80 pounds and shows no evidence of recurrence by either physical or roentgenologic examination.*

DISCUSSION

The interesting features are self-evident. Although malignancy is more common in older age groups, it is still one of the leading causes of death in

*Patient is alive and well at date of publication.

children and must always be entertained as a possibility in any protracted illness in children. The suggestively positive heterophil agglutination test must also be regarded with suspicion if it does not have sufficient fluctuation, as in a true glandular fever, and if exclusion tests are not run. Not enough can ever be said about repeated rectal and bimanual examinations, despite the fact that there is no abdominal complaint. The literature is at variance as to the most

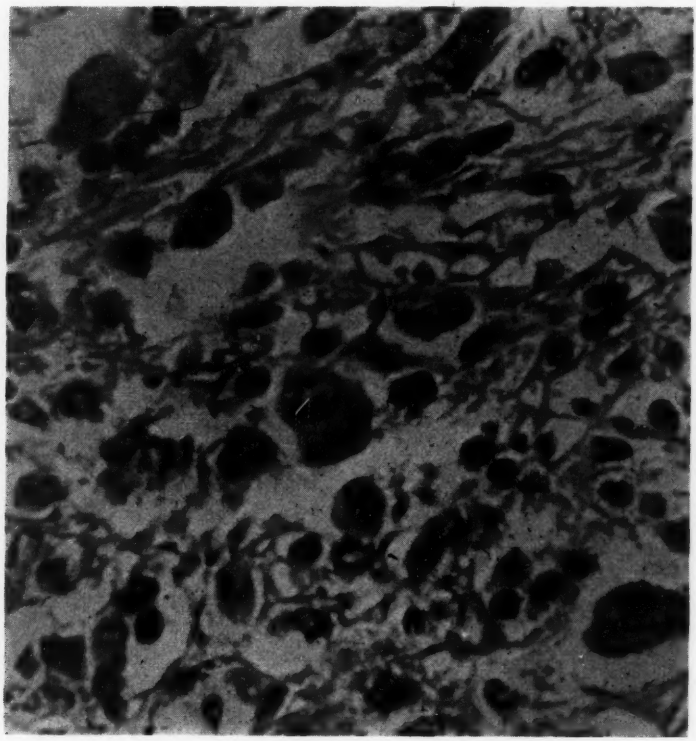

FIG. 3. Microscopic picture.

common sites and the prognosis of leiomyosarcoma. This is undoubtedly due to the relatively small number of cases that any one clinic can report.

Cameron reports the distal ileum and proximal jejunum as the more common sites, as does Maingot. In this case the site was in the distal jejunum.

As to prognosis, Kiefer reports 11 cases of small bowel malignancies, including carcinomas where 60% were resectable; operative mortality was 30%, and five year survival was only 5%. It is our impression that for the type of case presented, the prognosis is considerably better.

Conclusions

1. A case of leiomyosarcoma of the small bowel is reported in a seven and one-half year old girl with no complaint other than fever.
2. Some interesting features in diagnosis are presented.

Summario in Interlingua

Es reportate le caso de un puera de septe e medie annos de etate, admittite al hospital post tres septimanas de febre de indeterminate origine. Le patiente habeva nulle dolores abdominal, e le prime examines rectal e abdominal esseva negative. Un test de agglutination heterophile esseva positive lo que suggereva le suspicion de un mononucleosis infectiose. Nonobstante, repetite bimane examines rectal revelava finalmente un dur e rotunde massa movibile de circa 5 cm de diametro.

Per medio de laparotomia il esseva constatate que le massa esseva un leiomyosarcoma del jejuno distal con un area necrotic al base. Le subsequente operation effectuava un resection de 30 cm de jejuno con anastomose de termino a termino. Le patiente recuperava sin incidente e vive in bon valetude a iste tempore, plus que quatro annos post le intervention chirurgic.

Le autores signala que malignitate es un del principal causas de morte in juveniles in iste pais e debe esser prendite in consideration in omne maladia obscur. Es discutite le periculo de diagnoses erronee suggerite per un constatation laboratorial, e le necessitate de repetite examines physic es sublineate. Le autores opina que prompte diagnoses e adequate excisiones chirurgic establirea pro iste tumores prognoses multo plus favorabile que lo que es describite in le litteratura.

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EDITORIAL

THE PRESENT PLIGHT OF MEDICAL LITERATURE

"For let there be no mistake about it, this enormous proliferation, this pullulating and fungus-like growth is both a nuisance and a danger." (Hutchinson)[1]

There seems to be general agreement that medical "literature" has reached a glut of such proportions that unless it is controlled we shall all drown in the flood. Some 16 years ago Sir Robert Hutchinson wrote: "Must we sit still and see science suffocated in its own secretions, or can we do anything to mitigate the evil?" [1]

The approach to this problem should first involve some quantitative data. From an unofficial estimate by the Armed Forces Medical Library [2] it appears that perhaps 3,000 books in medicine and the allied sciences are published throughout the world in one year. This figure includes new titles and new editions. About 900 come from this country alone.

Lists from the Welch Medical Library Indexing Project, at Johns Hopkins University, show 6,369 titles of periodicals, of which some 4,454 are substantive, i.e., containing original articles, and not medical news bulletins, congressional proceedings and the like. Of this gradually increasing number of journals about 1,400 are published in the United States.

Another example of this plethora is that the *Current List of Medical Literature* indexed 109,274 separate articles in 1954. In fact the volume of medical writings has become so great that "it may prove quicker to re-discover a known fact than to search and find that fact in the published literature." [3]

The obvious evil result is that there is too much to read, and not enough time to read in. There are other difficulties in this situation, affecting many medical journals, and which may be briefly noted as follows: (a) financial: The income to journals from subscriptions and advertising must be spread thinner to cover the field; libraries, chronically impoverished, often cannot be truly representative. This dilution has resulted in some remarkably low circulation figures even for several very important publications. (b) scientific: Not only are there fewer readers per journal than need be, but many important observations, both here and abroad, are not seen by those who might best appreciate them. In fact, to reach a wider audience some authors "re-write" their papers for journals with a different group of subscribers—a fact that probably accounts for a sizeable fraction of the excess publications. The dilution of top-flight outlets also produces a problem of survival for some journals, especially in the specialties. In the case of a

[1] Hutchinson, Sir R.: Medical literature, Lancet **2**: 1059 (Nov. 18), 1939.
[2] Grinnell, M. E.: Personal communication.
[3] Dick, W. E.: Science and the press, Impact (UNESCO) **5**: 143 (Sept.), 1954.

particular journal, then, there may be a deficiency of papers of the highest caliber, a too-small circulation and non-existent advertising.

The causes of this serious situation are multiple. First, there is no doubt that some of the increase in publications is due to accelerated medical advances. The tremendous spurt in clinical and laboratory research, particularly in the last 10 or 15 years, has perforce resulted in many more publications. Research grants, governmental or private, are now available beyond the wildest dreams of a scientist vintage post World War I. To continue receiving grants, or to attract new ones, reports must be published.

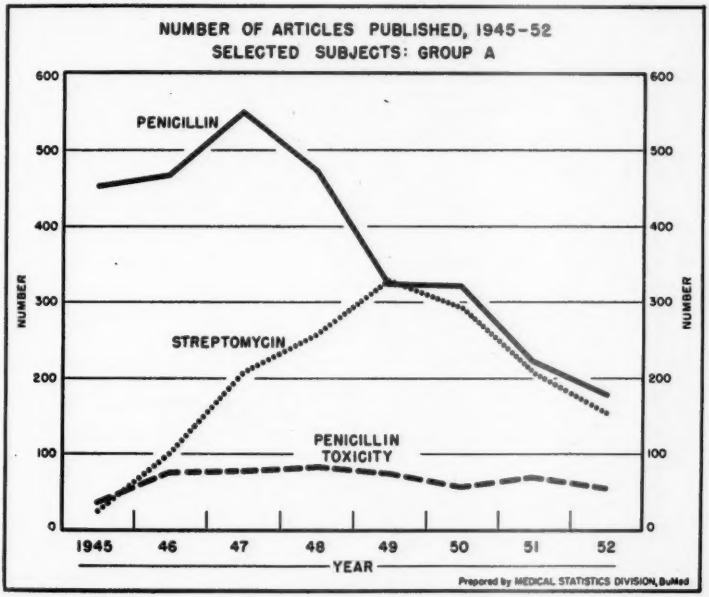

FIG. 1.

The effect of a new discovery on the medical literature may be judged from Bjorneboe's [4] experience that more than 8,000 papers on Aureomycin alone appeared in one year recently. Recently a survey was made based on the number of titles on an individual topic appearing in the *Quarterly Cumulative Index Medicus* for the post war period of 1945–1952 inclusive. These figures are based on classification by title and therefore are only representative of trends and not a precise count.

Figure 1 shows the rise, leveling off, and fall in the number of articles

[4] Bjorneboe, J.: Responsibility of the author and editor in preparing manuscripts for the press, World M. J. 1: 111 (Mar.), 1954.

on streptomycin. This is a typical curve for publications on new therapy. Also shown is the descending limb of the penicillin curve. It is pertinent to note that the number of articles on penicillin toxicity has not changed, suggesting that this problem continues to be a matter of considerable importance.

Figure 2 shows that the publication interest in malaria declined after the Second World War; on the other hand the discovery and subsequent research on vitamin B_{12} is reflected in the rise from 0 to 170 indexed articles in four years.

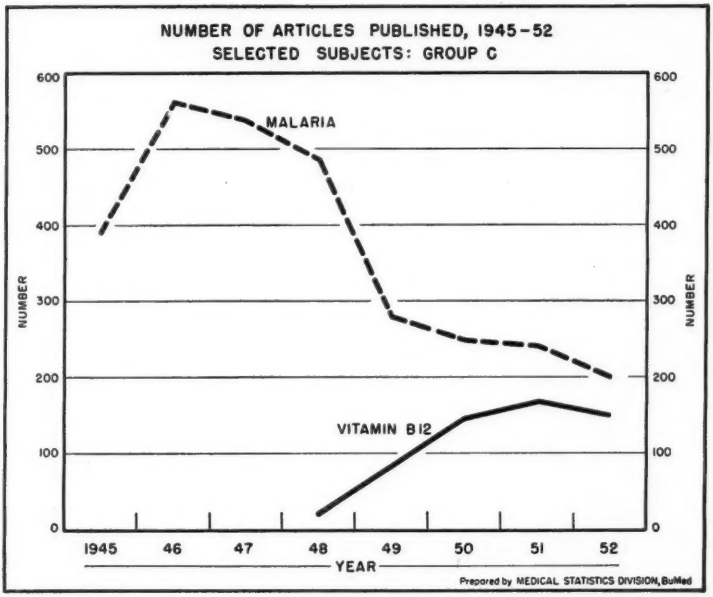

FIG. 2.

Figure 3 illustrates how papers on adrenocortical preparation jumped from less than 50 in 1945 to more than 1,100 in 1952. In comparison the number of papers on diabetic coma and the treatment of allergy remained comparatively stable. Thus it would seem that experience in hospital and clinic is rather closely reflected in medical periodicals.

Other reasons for the mushroom growth of literature are that publications are important to an individual who hopes to rise in the academic world. A bibliography helps in Specialty Board certification, which in turn gives one some advantages in military and Veterans Administration positions, and materially improves hospital staff appointments. These,

plus local prestige all lead to conscious or unconscious pressures to "write papers." This striving for recognition leads in some instances to the pernicious premature announcement of clinical and laboratory "data."

Furthermore, the development of many medical societies in recent times has often resulted in an "organ" which reports papers presented at meetings. Many medical societies (small in membership although homogeneous in interest) for one reason or another soon find themselves in the journal business.

What is to be done about the inundation? Hutchinson [1] recommended strict birth control of new journals, the amalgamation of many existing

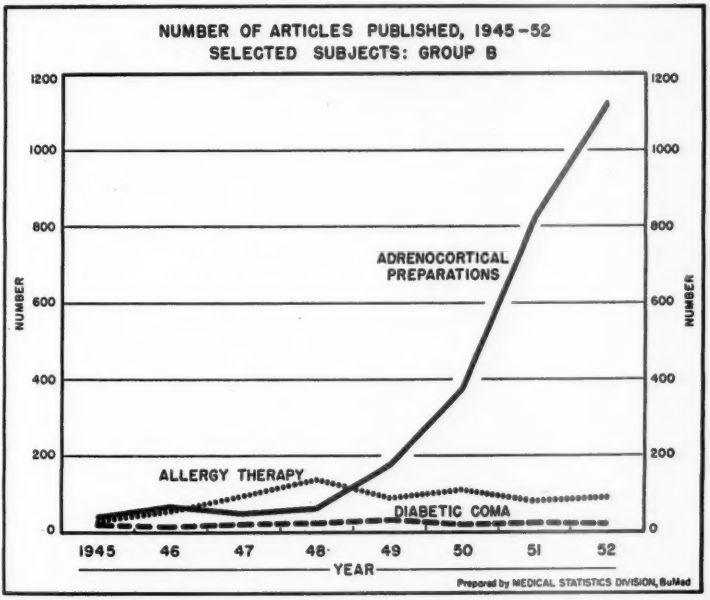

FIG. 3.

periodicals, with the abolition of certain "local and hospital" publications, because "superfluous journals lead to superfluous writing." These sweeping suggestions are impractical at present and perhaps not entirely justified.

Perhaps more to the point is his remark "Powerful astringents . . . may be required to check the verbal diarrhea which afflicts so many writers, but it is the business of the editor to administer them." [1]

A first step might well be a wide spread agreement of all medical editorial boards to follow Hewitt's [5] first commandment:

[5] Hewitt, R. M.: Exposition as applied to medicine, J. A. M. A. 156: 477 (Oct. 2), 1954.

"Thou shalt not, unless circumstances be extraordinary, release for publication a paper that neither contains anything new nor sheds new light on something old."

Even more germain would be a reduction in the weight given to a *quantitatively* impressive bibliography by the many organizations, now consciously or unconsciously basing their evaluation of a physician's worth on his "paper weight."

The present plight of medical literature is serious and a drastic remedy is clearly indicated.

S. O. Waife, M.D., F.A.C.P.

REVIEWS

Reactions with Drug Therapy. By HARRY L. ALEXANDER, M.D. 301 pages; 16 × 24 cm. W. B. Saunders Co., Philadelphia. 1955. Price, $7.50.

In this valuable book on drug hypersensitivity, defined by the author as "mechanisms that are responsible for lesions which differ from pharmacological effects or those of overdosage, and which are induced by therapeutic or subtherapeutic amounts," the author reveals some of the accumulated experience and knowledge of many years of practice and study. It is made clear early in the book that allergy is only a part, and perhaps a small part of this problem. The ever multiplying armamentarium of the physician makes it necessary for him to be aware of the potentialities of untoward effects of his therapeutic materials. The table of contents of this book makes one eager to read of the peculiar responses reported to many drugs not considered by the novice in this field particularly prone to produce reactions.

Good documentation is provided for the material presented and the substances discussed are organized into classes such as chemotherapeutic preparations, antibiotics, antiarthritic drugs, drugs used in cardiovascular disorders, antihistamines, and vitamins, to mention only a part of the content.

The discussion of the mechanism of sensitivity reveals the chaotic state of knowledge in the field. A chemical basis for sensitivity reactions is notably lacking, and the reader is referred to the meager pertinent literature on the subject.

Many of the names of chemical compounds are misspelled (six were found in reading this book), and there are some errors which require more careful editing in the next edition of this valuable book.

SAMUEL P. BESSMAN, M.D.

Letalfaktoren in ihrer Bedeutung für Erbpathologie und Genphysiologie der Entwicklung. By ERNST HADORN. 338 pages; 17.5 × 24.5 cm. Georg Thieme Verlag, Stuttgart; available in the U. S. A. and Canada from Intercontinental Medical Book Corporation, New York. 1955. Price, Ganzleinen DM 39.–

A "lethal factor" in the genetic sense may be defined as an inherited factor (gene or complex of genes) which leads to the death of an individual prior to the age of reproduction. In recent years, with the striking decrease in the relative importance of the infectious and contagious disease entities, such factors have emerged as a significant cause of prolonged morbidity and early death in man. In this book a distinguished Swiss student of the problem presents a masterful survey of lethal factors as they have been recognized and studied in a wide variety of plants and animals.

The first portion of the book is devoted to the formal genetics of lethal factors—their genetic basis, how they are transmitted, how they arise. Of particular importance to the physician is the concept that although many genes classified as lethal factors are lost each generation because of death prior to reproduction, other genes with similar effects arise in each generation because of mutation. Since there is at present no way known to decrease the baseline, spontaneous mutation rate in man, lethal factors will be with us for the foreseeable future. However, therapeutic advances offer the possibility of nullifying the effects of lethal factors, as illustrated by the case of cystic fibrosis of the pancreas in man.

The latter portion of the book deals with the problem of how lethal factors exert their effects—in single or double dose, at what stage of development, the specificity of the tissue involved, the behavior of explanted tissue containing lethal

factors, the experimental production of forms which resemble those due to lethal factors, and the biochemical basis of lethal factors. Although the majority of the illustrative examples is based on non-human material, since the analysis has been pushed farthest in such material, the author has cited examples from man where these exist and are pertinent.

The author's style is simple and clear. The book is well composed and superbly illustrated. References are up to date. This work will stand as a classic on the subject and is unhesitatingly recommended to the German-reading physician who desires an understanding of a subject of growing theoretical and practical importance.

JAMES V. NEEL, M.D.

Myocardial Infarction—Its Clinical Manifestations and Treatment with Anticoagulants—A Study of 1031 Cases. By IRVING S. WRIGHT, M.D., CHARLES D. MARPLE, M.D., and DOROTHY FAHS BECK, Ph.D. 656 pages; 17.5 × 26 cm. Published for the American Heart Association by Grune and Stratton, Inc., New York. 1954. Price, $8.50.

This book presents the highly detailed report of the Committee on Anticoagulants of the American Heart Association. It includes 1031 cases, of which 442 served as controls and 589 were treated with anticoagulants by responsible investigators in 16 coöperating hospitals. Patients admitted on an odd day of the month were started on anticoagulant therapy while those admitted on an even day served as controls. The diagnostic criteria and the anticoagulant program to be followed were carefully prescribed and a standard reporting procedure adopted.

There is available in the report of this exacting study a mass of statistical material of great value. In clearly presented tables and charts are summarized the clinical details, laboratory findings, past medical histories, thromboembolic complications, autopsy findings, hemorrhagic complications, and many other items of general and specific interest. There is also an appendix containing 91 supplementary tables including detailed autopsy findings of each case submitted to autopsy.

In the control group, 26.0% developed thromboembolic complications, while these appeared in only 10.9% of the treated group. The cases were further subdivided into good and poor risk groups with the authors concluding that even in the good risk cases there is an improved thromboembolic record with anticoagulant therapy. Of the control group 23.4% died, as compared to 16.0% of the treated group with the difference ". . . largely accounted for by the reduction in cases dying after the development of a thromboembolic complication." The recommendation is therefore made that "a substantial period of three to four weeks of anticoagulant therapy be given to patients with myocardial infarction, provided that no significant contraindications are present and that facilities are available for meticulous supervision of its administration."

This report is of considerable value not only for the results of anticoagulant therapy but for the wealth of information presented on myocardial infarction.

L. S.

A Textbook of Physiology. 17th Ed. Edited by JOHN F. FULTON, M.D., Sterling Professor of the History of Medicine, Yale University School of Medicine. 1275 pages; 16.5 × 25.5 cm. W. B. Saunders, Philadelphia. 1955. Price, $13.50.

This is the seventeenth edition of one of America's oldest textbooks of physiology and the third since the editorship was taken over by John F. Fulton. It continues the tradition established by him in 1946 and anyone familiar with the two previous editions will feel at home in this one. The format is substantially the same and the content has been revised only where it is necessary to bring it into conformity with

the latest physiological research. The section dealing with nervous activity has undergone the most extensive revision. Among other things, a new chapter on the limbic system has been added. Regrettably the chapter on the historical background of American physiology, a feature of previous editions, has been omitted. Perhaps this appeals more to the teaching physiologist than the medical student for whom the book is primarily written, but certainly five pages is not too high a price to pay for making at least an occasional student aware of, and perhaps even interested in, his debt to the past.

The title is to be commended for its honesty and forthrightness. It is a textbook of physiology, no more and no less. No attempt is made to make the book practical in the sense of trying to interpret disease states in terms of their physiology. Clinical material is introduced from time to time—never for its own sake, but simply to illustrate some physiological principle that might best be clarified in this way. While the style is not always as clear and simple as it might be, it is not so complex that the earnest student cannot read and study to his profit.

The book is somewhat unbalanced, a fault of the two preceding editions which has not been corrected. Almost one-half of the space is devoted to nervous activity and less than a tenth to the hormones. The chapter on electrocardiography is as long as the whole section on reproduction, which seems a bit disproportionate. However, these are not serious faults and certainly do not detract from the usefulness of the book. More importantly, it can be used by the practicing physician as an authoritative and reliable guide as to how today's physiologists think about the problems in their fields. As such it well deserves a place in the company of great physiological texts.

DIETRICH C. SMITH, M.D.

Surgery of the Caecum and Colon. By STANLEY AYLETT, M.B.E., M.B., B.S., B.Sc., F.R.C.S., Surgeon, The Westminster Hospital Teaching Group (Gordon Hospital). 295 pages; 17 × 25.5 cm. The Williams and Wilkins Co., Baltimore. 1954. Price, $9.00.

This is a well written, well illustrated monograph, whose title the author must have been at considerable pains to select. Exclusion of the anus leaves a text chock-a-block with useful information on all phases of major surgery of the large intestine.

Many of the basic principles of this branch of surgery have had an English origin, stemming largely from two schools whose ideas did not always correspond, but Mr. Aylett has taken the best from both, added some American and continental ingredients, and presented what may be considered a crystallization of the best of nearly all modern thought on his subject.

The numerous illustrations are in the best British tradition, and in all forms, whether drawings or photographs in color or in black and white, would be hard to improve upon. Statistics have been studiously avoided, and they will not be missed.

One might have wished that if anomalies of midgut rotation were to be included that mention were made of the commonest, in the form of plain non-rotation. The author is a little lavish in his extent of lengthwise removal of bowel. Following the ligation of arterial supply at the appropriate level, his approach to gut survival is probably a little pessimistic. The simple expedient of severing the marginal vessel to see whether it bleeds still has merit and may determine a more conservative course than the book indicates. No special stress has been attached to the wider removal of pericolic areolar tissue and retroperitoneal lymphatics as advocated and sometimes practiced in this country.

For all who are in any way interested in abdominal surgery, this most comprehensive and pleasingly written work is a must.

M. E.

Gourmet Cooking for Cardiac Diets. By FLORENCE FIELD; introduction by HAROLD FEIL, M.D. 350 pages; 15 × 22 cm. The World Publishing Company, Cleveland. 1953. Price, $3.50.

This book, by making the foods attractive and appetizing, may well serve to induce cardiac patients to follow a restricted intake of sodium. Here are numerous ideas for making taste-tempting dishes written by Florence Field, the wife of a doctor who has traveled widely in many European countries and is familiar with their exotic foods. The greatest portion of the book is devoted to low sodium recipes with the small remainder given to the recipes for the low fat, low cholesterol diet, and the low purine diet.

A more careful evaluation of this volume, however, discloses a book which should be used by the patient only under the close supervision of a doctor, dietitian, or nutritionist. When left to the choice of the patient, tasty recipes with low-sodium content would gain predominance over good nutrition and obtaining the correct number of calories. In this manner, the text might prove a disadvantage to the patient.

This should be a useful reference for the dietitian in planning interesting and tasty low sodium meals for patients. It is a valuable asset to have a low sodium cook book to refer to for variability in meal planning, and as an aid to the patient in staying on a low sodium diet.

A. L. H.

Tumors of the Major Salivary Glands (Atlas of Tumor Pathology, Section IV, Fascicle 11). By FRANK W. FOOTE, JR., M.D., Attending Pathologist, Memorial Center for Cancer and Allied Diseases, and EDGAR L. FRAZELL, M.D., Associate Attending Surgeon, Memorial Center for Cancer and Allied Diseases, New York, N. Y. 149 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. 1954. Price $1.50, for sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C.

This volume presents an analysis of 877 cases of tumors of the parotid, submaxillary and sublingual glands seen at the Memorial Center for Cancer and Allied Diseases during a 20 year period ending in 1949. The tumors are histologically classified with respect to specific tumor type and the distribution within the three major glands. The histogenesis of each group of related tumors is presented together with gross and microscopic descriptions supported by numerous well executed photomicrographs.

The reviewer feels that this material is well organized and supported by adequate bibliography. It constitutes an excellent reference to a significantly large number of cases of relatively uncommon tumors of the major salivary glands.

The fascicle would prove of benefit to the inquisitive student of pathology and surgery; and the pathologist and general surgeon would find the work of considerable value as a reference.

L. K.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Alcohol and Alcoholism: Report of an Expert Committee. World Health Organization Technical Report Series No. 94. 14 pages; 24 × 16 cm. (paper-bound).

1955. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Cardiolipin Antigens: Preparation and Chemical and Serological Control. World Health Organization Monograph Series No. 6. 2nd Ed. By MARY C. PANGBORN, Ph.D., J. O. ALMEIDA, M.D., F. MALTANER, Ph.D., A. M. SILVERSTEIN, Ph.D., and W. R. THOMPSON, Ph.D., Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. 52 pages; 24 × 16 cm. (paper-bound). 1955. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $1.25.

Clinical Biochemistry. 5th Ed. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, Jefferson Medical College, etc.; and MAX TRUMPER, Ph.D., formerly Lecturer in Clinical Biochemistry and Basic Science Coordinator, Naval Medical School, National Naval Medical Center, Bethesda, Maryland. 738 pages; 24 × 16 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $9.00.

Clinical Cytology, Using the May-Grünwald-Giemsa Stained Smear (in two volumes). By P. LOPES CARDOZO, M.D., Medical Superintendent, Bethel Hospital, Delft, etc.; with a chapter on Prostatic Cytology by J. POSTHUMA, M.B., Cytologist, Surgical Clinic, University Hospital, Leyden. 128 pages in Vol. I, 191 pages in Vol. II; 23.5 × 17 cm. 1954. L. Stafleu, Leyden, The Netherlands. Price, $19.50, free Baltimore.

Clinical Toxicology. 3d Ed. By CLINTON H. THIENES, M.D., Ph.D., Director, Institute of Medical Research, Collis P. and Howard Huntington Memorial Hospital, Pasadena, etc.; and THOMAS J. HALEY, Ph.D., Chief of the Division of Pharmacology and Toxicology, Atomic Energy Project, and Associate Clinical Professor of Medicine (Industrial Medicine), School of Medicine, University of California, Los Angeles. 457 pages; 20 × 14 cm. 1955. Lea & Febiger, Philadelphia. Price, $6.50.

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